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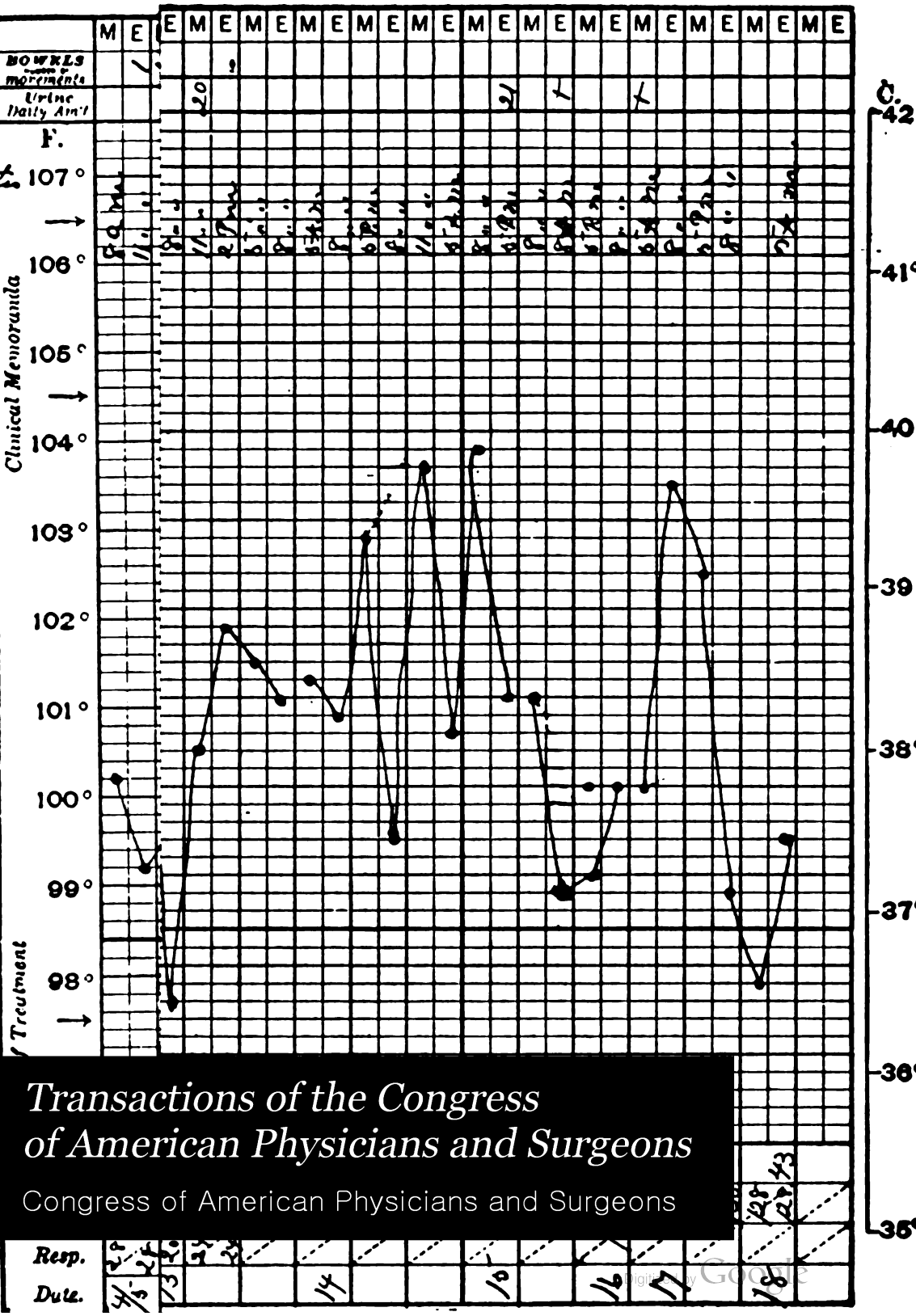

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TRANSACTIONS

OF THE

CONGRESS

OF

American Physicians and Surgeons.

SIXTH TRIENNIAL SESSION,

HELD AT

WASHINGTON, D. C.

May 12th, 13th and 14th, 1903.

PUBLISHED BY THE CONGRESS:

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MINUTES.

The sixth triennial session of the CONGRESS OF AMERICAN PHYSICIANS AND SURGEONS took place in Washington, D. C., May 12th, 13th and 14th, 1903.

The first meeting was held in the Columbia Theater on May 12th, the President, Dr. Wm. W. Keen, in the chair.

At 3 P. M. the President called the meeting to order and at the request of a Committee of the American Association for the Advancement of Science, of which Daniel C. Gilman, LL.D., is Chairman, called the attention of the Congress to the project of raising ($20,000) twenty thousand dollars for a permanent memorial to be erected in the City of Washington to the late Major Walter Reed, M.D., U. S. A., and his work. It was thereupon moved, seconded and carried that the President of the Congress be authorized to appoint a Committee consisting of one from each of the constituent societies of the Congress to bring the matter to the attention of his Society, and endeavor to raise funds for the purpose. The President stated that he would make the appointments after the adjournment of the Congress.

The Secretary announced that at the request of the Executive Committee a meeting for business would be held at 2.45 P. M., Wednesday, May 13th. He also read an invitation from the Management of the Cosmos Club to the members of the Congress to the privileges of the Club.

The President then announced that the subject for the consideration of the Congress was "The Pancreas and Pancreatic Diseases," and introduced Dr. Eugene L. Opie to read the first paper "on the Anatomy of the Pancreas." (Page 1.)

Prof. Russell H. Chittenden then read a paper "on the Physiology and Physiological Chemistry of the Pancreas." (Page 8.)

Prof. Simon Flexner said that as his paper "on the Etiology and Pathological Anatomy of the Pancreas" would take more than the allotted time to read, he would give an abstract of it. (The paper appears in full on Page 18.)

Dr. Reginald H. Fitz followed with a paper "on the Symptomatology and Diagnosis of Diseases of the Pancreas." (Page 36.)

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Prof. Johann v. Mikulicz-Radecki, of Breslau, Germany, by invitation of the Executive Committee, read a paper "on the Surgery of the Pancreas; with especial consideration of Trauma and Inflammatory Processes." (Page 55.)

Dr. Roswell Park then continued "on the Surgery of the Pancreas; with reference principally to Cysts, and other neoplasms." (Page 80.)

The subject was further discussed by Dr. Charles G. Stockton, Dr. Herbert U. Williams, Dr. Maurice H. Richardson and Mr. B. S. A. Moynihan, of Leeds, England. (Page 98, et seq.)

The meeting then adjourned.

The Congress assembled at 8 P. M. in old St. Matthew's Church, corner of H and 15th Sts., to listen to the address by the President of the Congress on "The Duties and Responsibilities of Trustees of Medical Institutions." (Page 228.)

The third meeting of the Congress was held in the Columbia Theater at 2.45 P. M. in Executive Session to act upon the following recommendation from the Executive Committee: "That the next session of the Congress be held in 1907 and triennially thereafter."

The President stated that the reason for this change was that the sessions of this Congress, and those of the International Medical Congress had lately been held in the same years, and in some instances the meetings had occurred so close together that difficulty was experienced, in that members who wished had been unable to attend both meetings, a fact to be deplored.

It was then moved, seconded and carried that the recommendation of the Executive Committee be adopted by the Congress.

The President announced that the Carnegie Institute at Washington, D. C., had undertaken the revival of the publication of the Index Medicus and stated that subscriptions thereto, ($5) five dollars per year, should be sent to that institution. He urged upon members of the Congress the importance of keeping up this unique publication.

At 3 P. M. the consideration of the scientific program was opened: the subject being "The Medical and Surgical aspects of the Diseases of the Gall Bladder and Bile Ducts."

Prof. C. A. Ewald, of Berlin, Germany, by invitation of the Executive Committee, read the first paper "On the diseases of the Gall Bladder and the Bile Ducts, with special reference to diseases of the Stomach and Intestines." (Page 105.)

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Dr. John H. Musser followed with a paper "On some medical aspects of the diseases of the Gall Bladder and Gall Ducts." (Page 121.)

Dr. George E. Brewer read a paper entitled "The differential Diagnosis of diseases of the Gall Bladder and Bile Ducts." (Page 143.)

Dr. C. A. Herter then spoke on "The Etiology and Pathology of Gallstones," and requested permission to print his paper in full, as it would take longer than the allotted time to read it. (Page 158.)

Dr. William J. Mayo then read a paper entitled "A study of five hundred and thirty-four operations upon the Gall Bladder and the Bile Passages." (Page 195.)

Prof. Hans Kehr, of Halberstadt, Germany, by invitation of the Executive Committee, then read a paper "On the Surgical Treatment of Obstruction of the Common Bile Duct by Stone or Tumor." (Page 203.)

The subject was further discussed by Drs. Frank Billings, George Dock, Henry Sewall, Edward G. Janeway and Mr. Moynihan. (Page 219, et seq.)

The Congress then adjourned *sine die*.

At an informal meeting of the Congress held for social purposes in the parlors of the New Willard Hotel on May 14th at 8 P. M., lantern slide demonstrations were given under the auspices of the Association of American Physicians on "Ring Bodies in the Blood of Anaemic Patients," by Dr. Richard C. Cabot, a member of that Association; and by invitation of the same Association, by Dr. G. C. Locke of Boston, Mass., on "Twenty-one cases of Paget's Disease (Osteitis deformans)."

Dr. Cabot's paper and illustrations appeared in the "Journal for Medical Research" for February, 1903.

In accordance with the resolution of the Congress passed on May 12th (above), the President appointed the following Committee on the Major Reed memorial: Dr. Lewellys F. Barker, Chicago, Ill., of the Association of American Physicians—Chairman; Dr. Chas. W. Kollock, Charleston, S. C., of the American Ophthalmological Society; Dr. B. Alexander Randall, Philadelphia, of the American Otological Society; Dr. James W. Putnam, Buffalo, N. Y., of the American Neurological Association; Dr. Joseph Tabor Johnson, Washington, D. C., of the American Gynecological Society; Dr. Henry W. Stelwagon, Philadelphia, of the American Dermatological Association; Dr. Henry L. Wagner, San Francisco, of the American

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Laryngological Association; Dr. William J. Mayo, Rochester, Minn., of the American Surgical Association; Dr. Fred'k I. Knight, Boston, of the American Climatological Association; Dr. Samuel Alexander, New York City, of the American Association of Genito-Urinary Surgeons; Dr. Ansel G. Cook, Hartford, Conn., of the American Orthopedic Association; Prof. Russell H. Chittenden, New Haven, Conn., of the American Physiological Society; Dr. Wm. Keiller, Galveston, Texas, of the Association of American Anatomists; Dr. L. Emmett Holt, New York City, of the American Pediatric Society; Dr. G. Alder Blumer, Providence, R. I., of the American Medico-Psychological Association; Dr. Harold E. Ernst, Boston, of the American Association of Pathologists and Bacteriologists.

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By Invitation of the Executive Committee.

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Professor of Internal Medicine in the University of Berlin, Germany.
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Organized, October, 1885.

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*Dr. Roswell Park,	Buffalo, New York.
*Dr. F. E. Peckham,	Providence, Rhode Island.
Dr. J. C. Pegram, Jr.,	Providence, Rhode Island.
Dr. J. L. Porter,	Chicago, Illinois.
*Dr. John Ridlon,	Chicago, Illinois.
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Dr. Wm. Powell Wilson,	Philadelphia, Pennsylvania.
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Organized, September 17, 1888.

This Association did not meet with the Congress of 1903.

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American Ophthalmological Society	166	..	1	94
American Otological Society	115	..	4	65
American Neurological Association	93	15	9	59
American Gynecological Society	89	..	23	58
American Dermatological Association ..	50	..	10	30
American Laryngological Association ...	74	29	1	47
American Surgical Association	123	..	15	84
American Climatological Association ...	145	8	3	88
Association of American Physicians	123	..	13	98
American Association of Genito-Urinary Surgeons	49	..	..	37
American Orthopedic Association	57	21	5	37
American Physiological Society	105	..	..	28
Association of American Anatomists	151	..	9	..
American Pediatric Society	56	..	..	38
American Medico-Psychological Association	356	..	21	126
American Association of Pathologists and Bacteriologists	161	..	..	64
	1913	73	114	953
Total members of the Congress		2100		
Guests and Visitors				72
Total in attendance				1025

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THE PANCREAS AND PANCREATIC DISEASES.

THE ANATOMY AND HISTOLOGY OF THE PANCREAS.

BY EUGENE L. OPIE, M.D.

Associate in Pathology in Johns Hopkins University.

In the brief time at my disposal I will review a few facts which have an important bearing upon the physiology and the pathology of the pancreas and will emphasize especially those which as yet have attracted little attention. The pancreas performing a variety of diverse functions is more complex in structure than the other glandular organs which it closely resembles. Pathological alterations have given importance to many anatomical details previously regarded as insignificant.

The earlier anatomists, among them Galen and Vesalius, gave, it seems, little thought to the organ, believing that it acted as a cushion to support and protect the adjacent structures, and it was not until the middle of the seventeenth century that the duct of the gland was discovered by Wirsung, who thus made possible a proper interpretation of its physiology. The organ has since been regarded as a type of secreting gland and to its study we owe many of the facts that have served to explain the process of secretion in general. The so-called salivary gland of the abdomen resembles the salivary glands of the mouth, but the peculiarities which characterize it have been known only since Langerhans in 1869 published his dissertation describing its minute structure. Yet until the last few years the histological structures which bear his name have attracted so little attention that their significance has remained obscure.

Few organs are subject to greater variation than the pancreas. Santorini and subsequent anatomists have shown that it is normally provided with an accessory duct which, in some cases, can act as an outlet for the pancreatic juice, should the larger duct be occluded. In different vertebrate species and even among members of the same species the ducts of the pancreas vary greatly, and until recently it has been believed that the embryonic origin of the organ is subject to equal irregularity, but evidence that is still accumulating has shown that development follows a plan which is common to all species of vertebrates.

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The organ makes its appearance as an outgrowth or bud upon the dorsal aspect of the intestinal canal at a point between the hepatic duct which has already appeared and what will subsequently become the stomach. A little later two additional embryonic buds develop at either side of the hepatic duct upon the ventral aspect of what is now the duodenum. The subsequent history of these rudimentary structures varies in different species. In man one of the two ventral outgrowths disappears, fusing, perhaps, with the other, so that the adult gland is formed by the union of a ventral part in contact with the bile duct and a dorsal part which forms the greater mass of the organ.

In accordance with this plan of development the gland is in most cases provided with two ducts, of which the larger, the duct of Wirsung, enters the intestine in company with the common bile duct. The smaller accessory duct, the duct of Santorini, terminates in a papilla situated nearer the stomach than that of the larger duct. I hope I will not seem to cite unnecessarily well known facts, if I recall the usual relation which exists between these two ducts. The duodenal orifice of the accessory duct is very minute; receiving branches from all sides, the duct increases in size and finally joins the duct of Wirsung, into which during life it doubtless pours its contents. Variations from this normal or usual type have been frequently noted. In many instances the two ducts fail to anastomose; at times that which is nearer the stomach, namely, the duct of Santorini, is larger than the duct of Wirsung; often the duodenal orifice of the accessory duct is obliterated, while occasionally one or other duct has not been found. More surprising, in view of the embryological relations already described, is the claim that the bile duct occasionally enters the duodenum in company with the duct of Santorini, while the duct of Wirsung enters the intestine at a point more distant from the stomach. In such case the dorsal embryonic bud, in which originates the duct of Santorini, could not have arisen from the duodenum at a point between the hepatic duct and what will become the stomach.

Are the variations to which the pancreatic ducts are subject in the adult explicable upon the supposition that the pancreas develops from three original buds which bear a constant relation to the bile duct? Of more practical interest is the functional significance of the two ducts and their relation to lesions of the liver and pancreas. In order to obtain data more accurate than those at present available, I have dissected the ducts after injection in one hundred sub-

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jects. The results of this examination, differing in some important particulars from those previously obtained, will be, I hope, of some interest.

Though the ducts varied considerably, there was no departure from the embryological type already described. Two ducts were present in every instance, but occasionally one or the other was so small that it was found with difficulty. The common bile duct always joined the duct of Wirsung, while the duct of Santorini, unaccompanied, entered the intestine at a level nearer the pylorus. In ten of one hundred instances the two ducts failed to anastomose within the gland, and in four additional subjects the two ducts were united by such a minute twig that they might be regarded as independent of one another. In twenty instances the duodenal end of the duct of Santorini was not patent. These figures show that in at least one-third of all individuals the duct of Santorini cannot act as an accessory outlet when the duct of Wirsung is occluded. Moreover, in a considerable number of specimens the orifice of the duct of Santorini, though patent, was so minute that its functional significance was slight, the accessory duct being functionally a branch of the larger channel. In eleven of one hundred specimens the duct of Santorini, on the contrary, was equal in size or larger than the duct of Wirsung, so that during life it was doubtless the outlet for a considerable, if not the larger part, of the pancreatic juice.

Since cholelithiasis and other changes in the biliary passages are frequently the cause of lesions of the pancreas, the relationship of the pancreatic duct to the common bile duct has assumed increased importance. The two ducts usually unite to form a short common channel, the diverticulum of Vater, which is subject to almost as much variation as the pancreatic ducts themselves. I have examined the orifice of the two ducts in one hundred specimens. In eleven instances no diverticulum was present and the two ducts entered the duodenum separately at the summit of the bile papilla. In the remaining cases the diverticulum varied in length from less than one to eleven millimeters, while in only thirty specimens did this measurement equal or exceed five millimeters. The duodenal orifice of the diverticulum of Vater had an average diameter of two and a half millimeters. The figures are cited to show that unless a calculus, which has become impacted within the orifice, be of very small size, it will completely fill the diverticulum and occlude both ducts that enter.

The pancreas consists of a duodenal part, the head, and a narrower body which constitutes the greater part of the organ and is not

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definable from the splenic extremity, designated the tail. This classical description should, I think, be somewhat altered, for the head, I find, consists of two well-defined lobes corresponding to the two ducts of the gland. The anterior and lower part of the head is tributary to the duct of Santorini and consists of lobules grouped about the duct and its branches. A second lobe is formed by a smaller mass of parenchyma disposed about the duct of Wirsung as it passes through the head of the gland, and is situated behind the larger lobe. In the specimens which I have examined a cleft filled by loose areolar tissue separates the two lobes and is demonstrated most readily after the gland has been placed in a hardening fluid. The adjacent lobular surfaces, when exposed, are as smooth and well-defined as the external surface of the gland. This interlobular cleft, in contact with the duodenum, lies midway between the two pancreatic ducts and its depth depends upon the distance from the duodenum at which the ducts anastomose.

Recent observations have disclosed a fact which, seemingly of little importance, serves to explain the occurrence of certain abnormalities of the gland. Within the papilla of the duct of Santorini, Helly has found in many individuals lobules of pancreatic parenchyma situated immediately below the duodenal mucosa. Occasionally provided with an independent duct which enters the duodenum near the orifice of the duct of Santorini, they constitute a true accessory pancreas. Studying the papilla in the embryo, Helly found that this pancreatic tissue originates at a very early period of development from lateral branches which bud from the duct as it passes through the mesoblastic layers of the intestinal wall.

This process, I believe, explains the occurrence of small masses of aberrant pancreatic tissue embedded in the wall of the stomach or of the intestine, at a variable distance from the pancreas. Such aberrant glands are by no means so rare as has been supposed. I have collected from the literature only twenty-two examples, but in eighteen hundred autopsies performed in the Pathological Laboratory of the Johns Hopkins Hospital this anomaly has been observed in ten cases. Nodules of pancreatic tissue one or two centimeters across have occupied the submucosa or muscularis of the stomach duodenum or jejunum. In seven cases the accessory gland was situated above the pancreas in the wall of the stomach or of the duodenum, and in three cases below the pancreas in the duodenum or in the jejunum. Of some importance, as will be shown, is the fact that in two instances two accessory glands occurred in the same individual.

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The earlier writers, notably Zenker, assumed that an aberrant gland arose from an accessory embryonic outgrowth or bud from the intestinal canal. The constancy with which the pancreas of all vertebrates develops from three definitely situated duodenal outgrowths has, however, made it improbable that in man such a fundamental process is subject to variation. At the same time, this multiple origin has suggested that one of the embryonic structures which normally disappears may persist as an accessory pancreas.

In one case from the literature and in two of my cases two aberrant masses of pancreatic tissue were situated either above the pancreas, as in my cases, or below the pancreas, as in the case of Zenker. The existence of more than one accessory gland cannot be explained by the persistence of one or more embryonic structures, for in my cases the pancreas itself had undergone normal development and was provided with two ducts. A more probable explanation is the following: At a very early period of embryonic life a lateral branch of the pancreatic duct entangled in the mesoblastic layers of the intestinal wall is, by longitudinal growth of the intestine, carried a variable distance from the pancreas and a new duct is formed in much the same way that the pancreatic duct regenerates after section. In confirmation of this hypothesis I have found pancreatic tissue in the papilla of the duct of Santorini in two cases—the only ones examined—in which aberrant glands were found in the wall of the stomach, and in one case in which an aberrant gland was situated in the jejunum, that is, below the pancreas, lobules of pancreatic tissue were found within the bile papilla about the duct of Wirsung as it entered the intestine. Here pancreatic tissue has been rarely, if ever, found.

Histology of the Pancreas.—The larger ducts of the pancreas are lined by high columnar epithelium. The cells which form the smaller ducts become lower and finally flat as the secreting acini are approached. The acini are composed of large cells containing zymogen granules which, as Heidenhain has shown, present characteristic variation during different stages of secretion. Within the lumen of each acinus Langerhans found cells which resemble those of the terminal ducts and represent, as it were, an invagination of the duct into the lumen of the acinus. The nature and the significance of these centro-acinar cells is not known. Of greater importance are the structures to which their discoverer's name has been given, the so-called Islands of Langerhans.

Scattered amongst the secreting acini, several times the size of a single acinus, they are round or oval bodies composed of polygonal

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cells grouped together to form short, tortuous columns, which unite with one another in such a way that space is left for a network of wide capillary blood vessels. If the blood vessels of the pancreas are injected, glomeruli of tortuous dilated capillaries represent the capillary vessels of the interacinar islands, and though they have a superficial resemblance to the glomeruli of the kidneys, unlike the latter, they freely communicate by numerous anastomoses with the capillary network of the surrounding tissue.

The interacinar islands have been found in many species of mammals, birds and amphibia. For a time it was claimed that certain species did not possess them, but extended comparative studies have demonstrated the occurrence of analogous structures in all higher vertebrates and in a constantly increasing number of reptiles and fish.

The embryological studies of Lagnesse and others have shown that the cells which form the islands of Langerhans have a common origin with those of the secreting acini, and in the syphilitic pancreas of the fœtus I have found that the columns of the island as a result of retarded development are continuous with the small ducts of the gland. When, however, the organ has completed its development the islands are wholly independent of the secreting elements and it is not possible to trace a communication between the ducts of the gland and the interacinar islands.

The islands of Langerhans consist of columns of cells in intimate relation to a rich vascular supply and, having no communication with the pancreatic ducts, resemble in structure certain ductless glands, the parathyroid bodies and the adrenal glands and somewhat less closely the thyroid glands. Common to all vertebrate species, they doubtless have some important function. Independent of the secreting elements of the gland, they are not concerned in the elaboration of the pancreatic ferments. The relation of their cells to a rich vascular supply suggests that their action is through the medium of the blood. Abundant evidence in accord with these facts has shown, I believe, that the islands of Langerhans exert that influence upon carbohydrate metabolism which was formerly attributed to the pancreas as a whole.

In the human pancreas as in the human liver the lobules of the gland are not sharply defined, but in certain lower animals they are more clearly outlined by septa of connective tissue. In the pancreas as in many other organs the smallest lobule constitutes a unit of structure which repeats itself throughout the parenchyma. In

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the pancreas of the cat, for example, such a lobule outlined by connective tissue consists of a group of acini drained by a single duct; in some parts of the gland every lobule contains near its center an island of Langerhans. From the small arteries and veins which lie in the periphery of the lobule capillary vessels penetrate between the acini; several wide capillaries supply the rich vascular network of the island of Langerhans.

In man the individual lobules are often so fused together that their outlines are not discernible, but in general the same plan of structure exists. Of some importance is the fact that islands of Langerhans are not equally abundant in all parts of the gland. Actual count demonstrates that they are about three and a half times more numerous in the splenic extremity of the gland than elsewhere. In the pancreas from different individuals, moreover, the number varies considerably, and it is possible that in some instances as the result of a congenital defect the interacinar islands are too few to exert a normal influence on carbohydrate metabolism. In the pancreas of a child who died with diabetes the number of islands of Langerhans was almost a third of that usually present; the disease in this case was hereditary and affected six members of the same family. It suggests the possibility that diabetes may occasionally be the result of a congenital anatomical defect in the gland. The evidence in favor of such an hypothesis is at present inconclusive.

In conclusion, I may say, that two anatomical peculiarities of the pancreas, I believe, have not as yet received the attention they deserve from the physiologist, the pathologist, and the clinician. In the first place, the organ consists of two functionally diverse elements,—on the one hand, cells which supply to the intestine important digestive ferments, and on the other hand, cells having no communication with the ducts of the gland but in intimate relation to the blood vessels. In the second place, the close anatomical relation of the pancreatic duct to the common bile duct favors the transmission of morbid processes from the liver and bile passages to the pancreas.

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THE PANCREAS AND PANCREATIC DISEASES.

THE PHYSIOLOGY AND PHYSIOLOGICAL CHEMISTRY OF THE PANCREAS.

BY RUSSELL H. CHITTENDEN, PH.D.

Professor of Physiological Chemistry and Director of the Sheffield Scientific School of Yale University.

The striking advance made of late years in our knowledge of the structure and activity of the various glandular organs of the body emphasizes how great may be the complexity of function of individual tissues. We have long since passed that stage in our study of the physiology of a specific organ when we were content with the discovery of a single line of action. To-day we have learned that complexity of function is the rule rather than the exception, for not only may a given organ show a complexity of function truly appalling, but there are in addition inter-relationships between neighboring tissues which increase the field of action of any one structure. Nowhere is this general physiological truth better illustrated than in the pancreas. Recognized by De Graaf in 1664 as a gland from which a true secretion could be obtained by a suitable fistula, it was given scant attention until Eberle, in 1834, pointed out that an aqueous infusion of the gland had the power of emulsionizing fats; a fact which Claude Bernard in 1846 verified and amplified in his celebrated researches on the fat-digesting power of the pancreatic juice. Just prior to this later date, in 1845, Bouchardat and Sandras had called attention to the starch-digesting power of the pancreatic juice, clearly proving in their later experiments the existence of an amylolytic enzyme. In 1836 Purkinji and Pappenheim apparently discovered that the pancreas manufactures a proteid-dissolving agent, which later, in 1857, Corvisart verified, and clearly established the proteolytic power of the pancreatic secretion. So gradually there accumulated knowledge of the three-fold digestive power of the pancreatic fluid, involving the simultaneous formation in the gland cells of three distinct enzymes or their antecedents, each one endowed with the ability to digest one of the three classes of foodstuffs. To-day we clearly recognize the physiological importance of the amylolytic, adipolytic and proteolytic action of the pancreatic secretion, but we also understand with equal clearness that the manufac-

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ture of pancreatic juice is only one of the functions of this important gland.

If, for example, the pancreatic secretion is diverted from the intestine by a cannula introduced into the duct of Wirsung, no serious results follow; digestion, especially of fats, may be somewhat impaired, but there is no noticeable change in the general nutrition of the body. If, on the other hand, as von Mering and Minkowski pointed out a few years ago,[1] the pancreas is removed from the abdominal cavity, then a very decided change occurs, especially in the metabolism of carbohydrates. Indeed, so great is the derangement of carbohydrate metabolism in the body that a permanent glycosuria or diabetes results, which is soon followed by the death of the animal upon which the experiment has been performed. Equally noteworthy is the fact that if a small portion of the pancreas is left intact, or if the gland after excision is transplanted under the skin or elsewhere, the carbohydrate metabolism remains unchanged, from which we infer that there is manufactured in the pancreatic gland a substance or substances, which passing from the gland into the blood exercise some potent influence upon carbohydrate metabolism. Hence, as Stephen Paget has written,[2] "the pancreas is no longer taken to be only a sort of salivary gland out of place; over and above the secretion it pours into the intestines, it has an 'internal secretion,' a constituent of the blood; it belongs not only to the digestive system, but also, like the thyroid gland and the supra-renal capsules, to the whole chemistry of the blood and the tissues."

In still later days we have learned from the experiments of Blum[3] that glycosuria can be produced in dogs and rabbits by the introduction subcutaneously of extracts of the adrenal gland, but as Dr. Herter[4] has shown, this so-called adrenal diabetes is due to an action of the adrenal constituents upon the pancreas, hence we are led to believe that this adrenal glycosuria is the result of a modified pancreatic function. To-day we accept as clearly demonstrated, to quote Dr. Flexner,[5] "that the pancreas is the most important organ in the

[1] Archiv f. exper. Pathol. u. Pharm., Band XXVI, p. 371, 1889. Also, Band XXXI, p. 85, 1892.

[2] Stephen Paget: Experiments on Animals. Revised Edition. Putnam's Sons, 1903, p. 46.

[3] Deutsches Archiv f. klin. Medicin, Band LXXI, 1901; and Pflüger's Archiv f. Physiol., Band XC, p. 617, 1902.

[4] The Medical News, vol. LXXX, p. 201, 1902; and Virchow's Archiv, Band CLXIX, p. 479, 1902.

[5] Quoted from Simon Flexner, M.D. Annual address in Medicine. Transactions Wisconsin State Medical Society, vol. XXXVI, p. 60, 1902.

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body which presides over carbohydrate metabolism. It is perhaps not the only organ in the body concerned with this metabolism, for there is evidence that goes to show that the liver and perhaps other organs take part; but it is apparently the only organ which we cannot dispense with, as the president, so to speak, of that particular metabolic function; that if the liver fails, if the kidneys fail, if the central nervous system fails, and the pancreas remains intact, a readjustment may take place, but all the evidence is to the effect that the pancreas is essential; that when it fails, none of these other organs can vicariously step in and preserve the perfection of the metabolism, and therefore prevent the development of the symptoms of diabetes."

Still another indication of the close dependence of the pancreas upon other organs for the maintenance of its functional activity is seen in the recent work of Bayliss and Starling,[1] who find that the normal secretion of pancreatic juice is induced by the action of a specific substance termed *secretin* formed in the mucous membrane of the duodenum out of an antecedent substance called *prosecretin.* As is well known, the secretion of pancreatic juice is normally evoked by the entrance of chyme into the duodenum and is proportional to the amount of acid present. This secretion does not depend upon a nervous reflex, for it occurs when all the nervous connections of the intestine are destroyed. Contact of acid with the epithelial cells of the duodenum causes in them the production of a body (secretin), which is absorbed from the cells by the blood current, and is then carried to the pancreas where it acts as a specific stimulus to the pancreatic cells, exciting a secretion of pancreatic juice proportional to the amount of secretin present. So that, assuming this statement to be correct, the secretion of pancreatic juice is dependent upon the activity of the duodenal cells where the so-called secretin is manufactured; another evidence of the general truth of our statement that the functional activity of a gland is often dependent in no small degree upon the harmonious working of some related structure. Further, we might call to mind the action of the enterokinase of the intestinal secretion which, according to Pawlow, is a necessary factor in developing out of the zymogen of the pancreatic secretion an active proteolytic enzyme; a simple illustration of another phase of physiological interdependence.

With this preface, let us consider in greater detail some of the more important facts bearing upon the relation of the pancreas to

[1] Journal of Physiology, vol. XXVIII, p. 325, 1902; also, vol. XXIX, p. 174, 1903.

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carbohydrate metabolism. The statement that extirpation of the pancreas is speedily followed by the appearance of diabetes renders it quite clear that the glycosuria is the direct or indirect result of the suppression of a distinct glandular function. This withdrawal of the pancreas causes either an increased production of sugar in the body or else there is an inhibition of the process by which sugar is burned or consumed in the body. In conformity with the latter view, Lépine[1] has sought to show that the pancreas produces a specific glycolytic enzyme or ferment which it gives up to the blood, and which normally breaks down sugar into simple decomposition products. When the pancreas is extirpated then naturally, owing to the absence of this enzyme, sugar accumulates in the blood, hyperglycaemia results, followed by diabetes. Herzog,[2] however, by carefully conducted experiments, failed to find any conclusive evidence of a dextrose-splitting enzyme in the pancreas, thereby confirming similar conclusions arrived at by earlier workers, but Simácek has just succeeded in isolating a true glycolytic enzyme from the pancreas capable of splitting sugar into alcohol and carbonic acid.[3] There is, indeed, no question to-day that glycolytic enzymes are present in greater or less extent in many of the tissues and glands of the body,[4] as well as in the blood, but the pancreas is apparently not greatly distinguished above the other tissues in this respect, surely not in such degree as to account for the marked glycosuria following pancreas extirpation.

Chauveau and Kaufmann, on the other hand, have claimed that the internal secretion of the pancreas in some fashion acts upon the liver, thereby regulating the production of sugar. This theory presupposes that the sugar, which causes hyperglycaemia, is of hepatic origin and that it comes directly from the hepatic glycogen. In this connection it is to be noted that dogs fed on a meat diet, with the pancreas removed, may excrete 2.8-3.0 grams of dextrose in the urine for every gram of urinary nitrogen, and that in spite of the large content of sugar in the blood, glycogen formation is greatly reduced. Indeed, neither on a proteid diet nor by feeding an excess of grape sugar can the glycogen content of the organs of the depancreatized body be essentially increased.[5] Minkowski believes

[1] See Wiener med. Presse. 1892, Nr. 27–32.

[2] Hofmeister's Beiträge zur chemischen Physiologie. Band II, p. 102, 1902.

[3] Centralblatt für Physiologie. Band XVII, p. 3, 1903.

[4] As to the presence of zymase in animal tissues. See Stoklasa, Centralblatt für Physiologie. Band XVI, p. 652, 1903.

[5] Compare Cremer, Ergebnisse der Physiologie. Erster Jahrgang, I, p. 878, 1902.

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that in pancreatic diabetes the organism has practically lost the ability to decompose dextrose and that its excretion through the urine is a purely physiological process analogous to physiological glycosuria. Further, according to Minkowski, after total extirpation of the pancreas, decomposition of dextrose in the body may be *completely* suspended. In one experiment with a dog whose pancreas had been removed there was occurring on a meat diet an excretion of 3 grams of sugar in the urine, but the addition of 75 grams of dextrose to the diet was followed on one day by the appearance of over 74 grams of sugar in the urine, plainly indicating that the body had entirely lost the power of burning the carbohydrate. Undoubtedly to-day practically all physiologists are agreed that when the pancreas is extirpated, the resultant hyperglycaemia and glycosuria are due mainly at least to the inability of the organism under these abnormal conditions to decompose the sugar formed in or introduced into the body, but as to the exact explanation of the causes leading to this condition satisfactory proof is lacking.

It is quite within the province of physiology, however, to enquire whether the simple withdrawal of sugar from the metabolism of the body is sufficient to account for the symptoms of diabetes. Is it not more probable that the excess of sugar in the circulation and permeating the tissues exerts some disturbing or toxic influence, or that such influence is exerted by some products derived from this excess of sugar? This question has just been carefully investigated by Dr. James Scott[1] of Edinburgh, who studied the influence of subcutaneous injections of large quantities of dextrose on the metabolism of the dog. The method of subcutaneous injection was followed since it more nearly imitates the condition in diabetes, the sugar having time to act upon the tissues prior to its excretion, instead of being dealt with directly by the liver as when taken by the mouth, or rapidly excreted as when injected directly into the blood. The results of the experiments show that when dextrose in quantities ranging from 5 to 7 grams per kilo of body-weight is introduced subcutaneously into dogs in nitrogenous equilibrium, there is produced a marked increase in the excretion of nitrogen, this being due to an increased disintegration of proteids in the body and not to any alteration in the absorption of proteids. Further, in some instances there was observed a marked increase of ammonia in the urine under the influence of the dextrose, indicating that the latter is oxidized or decomposed in some manner by which acids result, or that the

[1] Journal of Physiology, vol. XXVIII, p. 107, 1902.

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increased proteid disintegration is accompanied by the liberation of acids. In this connection it will be recalled that von Noorden and others have emphasized the increased excretion of ammonia in diabetes. Dr. Scott concludes from his experiments that dextrose or more probably an acid derivative of dextrose causes a marked increase in proteid metabolism, acting like such toxic agents as phosphorus, etc., poisoning the protoplasm. There likewise results a diminution in the proportion of nitrogen built up into urea, the subcutaneous introduction of dextrose producing in this respect an effect similar to that induced by diphtheria toxine, or drugs such as sulphonal which interfere with the katabolic processes of the body. In this connection it is interesting to note that Kossa[1] some years ago observed that the subcutaneous introduction of cane sugar in dogs and rabbits caused a marked increase in the total amount of nitrogen, urea, and ammonia in the urine, which continued for some time after the administration of the sugar, and was associated with great emaciation of the animals.

It is quite probable, however, that with the pancreas extirpated many abnormalities occur, of which as yet we have little knowledge. Thus Nebelthau[2] has recently shown that in dogs with extirpated pancreas, the resultant diabetic organism can form sugar out of the by-products of proteid decomposition. Experimenting with such animals, he finds that plasmon, asparagin, acetamid, and other like substances, cause an increase in the sugar output. Further, where there is an interference with the normal oxidation of dextrose in the body, as may well occur after extirpation of the pancreas, bodies more or less toxic may be formed in undue amounts with a resultant disturbance of physiological equilibrium. Thus Hildebrant[3] has recently found that when rabbits are fed on oats for a long time and then fed dextrose, they die of oxalic acid poisoning. The explanation is that oxalic acid is a product of the incomplete oxidation or combustion of dextrose. Under ordinary conditions it is rendered harmless by combining with calcium, but on a long continued oat diet with a deficiency of calcium, the body loses its antitoxic element and thus the dextrose is rendered effective as a poison. Milk sugar, on the other hand, does not behave in this manner, since it does not yield oxalic acid. Sugars, such as dextrose, may oxidize to glycuronic acid and then to oxalic acid, etc., as Mayer[4] has pointed out.

[1] Pflüger's Archiv f. Physiol. Band LXXV, p. 310, 1899.
[2] Münchener med. Wochenschr. June 3, 1902.
[3] Zeitschr. f. physiol. Chem. Band XXXV, p. 141, 1902.
[4] Zeitschr. f. klin. Medizin. Band XLVII, p. 67, 1902.

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The liver indeed has the power of forming oxalic acid from glycuronic acid. Doubtless diabetes involves among other things interference with this oxidation.

Just here it may be well to observe that the cells of the pancreas have several peculiarities of composition worthy of note. Thus, the pancreas, as Grund[1] has shown, contains far more combined pentose than any other organ in the body. This 5-carbon atom sugar exists in the pancreas as a part of the cell nucleproteid, and according to Neuberg[2] it is l-xylose. It may be mentioned in passing that the discovery by Salkowski of pentosuria leads naturally to the supposition that in these cases the urine pentose comes from the pentose-bearing nucleoproteid of the organ as a result of some abnormal decomposition. E. Ebstein[3] has found that the fresh human pancreas contains 0.225 per cent. of l-xylose in combination, while the pancreas of animals contains as much as 0.447 per cent. of this same xylose, provided the glands are fresh. If, however, the glands are allowed to putrefy, the xylose rapidly disappears. The carbohydrate group in the pancreas nucleoproteid is in reality a component part of the nucleic acid of the pancreas, viz., the guanylic acid. This peculiar acid, as Ivar Bang[4] has shown, splits upon decomposition into numerous new bodies, viz., 35 per cent. of guanin, a purin base; 30 per cent. of a reducing sugar calculated as dextrose, in reality xylose; 17.5 per cent. of phosphoric acid (P_2O_5) and 13.5 per cent. of nitrogen-free substances, mainly glycerine. This means that the pancreas nucleic acid is made up of four molecules of guanin, three molecules of a 5-carbon atom sugar, xylose, three molecules of glycerine and four molecules of phosphoric acid, the two latter existing as a glycerophosphoric acid. Bang[5] has also found that this guanylic acid, when injected into the blood of dogs, has an anticoagulating action, causing also a lowering of blood-pressure, forced respiration, a tendency toward narcosis, alkaline reaction of the urine, a speedy appearance of albuminuria, and in one instance glycosuria. In this connection it may be noted that Salkowski and Neuberg[6] have shown the possibility of transforming 6-carbon atom sugars as dextrose into 5-carbon atom sugars such as xylose. This can be done outside the body by simple putrefaction, starting with

[1] Zeitschr. f. physiol. Chem. Band XXXV, p. 111, 1902.
[2] Berichte d. deutsch. chem. Gesellsch. Band XXXV, p. 1467, 1902.
[3] Zeitschr. f. physiol. Chem. Band XXXVI, p. 478, 1902.
[4] Zeitschr. f. physiol. Chem. Band XXVI, p. 133, 1898.
[5] Ibid. Band XXXI, p. 411, 1900.
[6] Zeitschr. f. physiol. Chem. Band XXXVI, p. 261, 1902.

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glycuronic acid, the first oxidation product of dextrose. By this method CO_2 is evolved, and the 6-carbon atom carbohydrate is changed in part into xylose, thereby suggesting a possible method of formation of the pancreas-nucleoproteid carbohydrate. Just here it may be interesting to note that A. Croft Hill[1] has recently called attention to the synthetic action of pancreatic ferments on glucose, the action being exactly analogous in this respect to that of yeast and Taka-diastase. This polymerisation of glucose is a strictly reversible process, in which we have a peculiar selective action of the enzymes, determined in part by changes in dilution, etc., but always in the direction of chemical equilibrium. In this specific instance the statement means that while pancreatic juice, from its contained enzyme glucase, has the power of forming glucose, this same sugar may by the reversible action of the same enzymes be synthesized into maltose, and indeed into other sugars.

Lately we have learned much concerning the development of enzymes in the body, and especially the influence of changed conditions upon the possible formation of new enzymes or modification in the proportion of already existing enzymes. Thus Pawlow[2] has clearly demonstrated the marked influence of the diet upon the volume, concentration and digestive power of the pancreatic juice secreted. A bread diet, owing to its richness in starch, leads to the secretion of a pancreatic juice exceedingly rich in amylolytic enzyme, while with a meat diet the amount of amylolytic enzyme drops at once to one-third that contained in the so-called "bread juice." We now accept without question the dictum that pancreatic juice, like other digestive secretions, is modified in composition by the character and amount of the food. A starchy food calls forth a pancreatic juice rich in starch-digesting enzyme; a food containing an abundance of fat leads to the secretion of an excess of the fat-splitting enzyme, while a rich proteid diet calls forth the proteolytic enzyme. With this statement before us, we are quite prepared to believe in the manufacture of a specific enzyme to meet changed conditions of diet. This indeed Weinland[3] has proved to be a possibility, for he finds on feeding milk for long periods to young and adult dogs, there is produced in the pancreas in increasing quantities a milk-sugar splitting enzyme, lactase, which

[1] Journal of Physiology, vol. XXVIII, p. xxvi, 1902.

[2] Compare 'Die Arbeit der Verdauungsdrüsen.' Vorlesungen von Prof. J. P. Pawlow. German edition by A. Walther. 1898. p. 48.

[3] Zeitschrift f. Biologie. Band XXXVIII, p. 607, 1899; and Band XL, p. 386, 1900.

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breaks up the sugar into dextrose and galactose. The same thing likewise happens on feeding milk-sugar alone, without the milk. In view of these facts, it is not at all difficult to conceive of an alteration of enzymes or enzyme action in the body in connection with a disturbance of pancreatic function which may be, in some measure, responsible for the unburned sugar as in pancreatic glycosuria. Surely, with the pancreas extirpated, there must be many deviations from the ordinary metabolic processes of the body. Thus recently Lépine and Mallet[1] have called attention to the fact that while in ordinary glycosuria there is no increase in the amount of sodium chloride excreted through the urine, yet in the glycosuria which follows extirpation of the pancreas there is a noticeable increase in the output of this saline constituent of the urine; a fact perhaps of no great physiological significance, and yet in harmony with what might be expected in the altered nutritional rhythm of the body.

How far is there justification for the belief that the pancreas controls carbohydrate metabolism through a specific internal secretion manufactured within any or all of its epithelial cells? That the pancreas exercises a controlling influence in some fashion is perfectly clear, but that it is a *direct* influence due to the direct action of some specific substance is less apparent. In thyroidectomized animals there is a decided amelioration of symptoms on feeding thyroid glands, or by using iodothyrin, but in de-pancreatized dogs the feeding of pancreas or the use of pancreatic preparations is without effect upon the glycosuria. Georgiewski,[2] for example, has found that the use of pancreatic preparations in diabetes does lead to an improvement in general conditions, which he attributes to better oxidative processes, but there is no effect on the glycosuria in dogs with the pancreas extirpated.

Most suggestive in its bearing upon the general question before us is the work of Dr. Herter[3] and his co-workers, Dr. Richards[4] and Dr. Wakeman,[5] primarily in the study of adrenalin glycosuria, but leading directly into the domain of pancreatic glycosuria. For, as Herter and Richards have pointed out, when a solution of adrenalin chloride is applied directly to the surface of the pancreas, there results a violent glycosuria of the same nature as that produced by

[1] Comptes Rend. Soc. de Biol. Tome LIV, p. 404, 1902.

[2] Botkin's klin. Zeitung. 1896. No. 41, p. 1022.

[3] The Medical News, vol. LXXX, p. 201, 1902; American Medicine, vol. III, p. 771, 1902; The Medical News, Oct., 1902.

[4] Amer. Jour. Physiol., vol. IX, 1903.

[5] Amer. Jour. Med. Sciences, vol. CXXV, p. 46, 1903.

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the peritoneal or subcutaneous injection of adrenalin. In other words, so-called adrenalin glycosuria is really of pancreatic origin, and further, as Herter and Wakeman have shown, there are a comparatively large number of substances aside from adrenalin which, when applied to the surface of the pancreas, likewise give rise to glycosuria. The one quality common to all of these substances is a reducing activity. Hydrocyanic acid, however, has no reducing power, but if applied in very dilute solution to the surface of the pancreas speedily causes glycosuria. This is to be explained on the ground of its exerting a specific action on animal cells, preventing the latter from absorbing oxygen, and with an absence of the normal amount of oxygen in a cell, an excess of reducing substances would naturally result. With this fact before us, we may certainly assume the possibility of glycosuria resulting from the action of many reducing substances when the latter come in contact with the cells of the pancreas, the action being a direct effect on the secreting cells of the gland, or indirect through an influence exerted on the metabolic processes of the structure.

"If this view of the matter is correct (to quote from Dr. Richards), an important relationship suggests itself between this form of experimental glycosuria and conditions in the human organism which may give rise to an excretion of sugar. The fact that many organs of the body may form reducing substances capable of easy oxidation which may reach the pancreas in the blood stream, carries with it the possibility that if the normal balance between the amount of these substances and the oxidizing power of the pancreas be disturbed, the production of glycosuria may occur."[1]

[1] Quoted from the article by Vosburgh and Richards. Amer. Jour. Physiol., vol. IX, March, 1903.

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THE PANCREAS AND PANCREATIC DISEASES.

THE PATHOLOGY OF PANCREATITIS, DIABETES AND FAT NECROSIS.

BY SIMON FLEXNER, M.D.

Professor of Pathology, University of Pennsylvania.

I have chosen to restrict my contribution to this symposium upon the pancreas and pancreatic diseases to three pathological conditions, which either affect the pancreas itself or are bound up with pathological states of that organ. The time limit for each paper making a full presentation of the "Pathology and Pathological Anatomy" of the pancreas impossible, I shall have to content myself with a brief consideration of pancreatitis, diabetes and fat necrosis. My labor has been greatly lessened, it is only fair to say, by the appearance within the past few years of Oser's monograph on the diseases of the pancreas, and very recently of Opie's work on the same subject. I have not hesitated to use these works freely in the collection of facts, and I take this opportunity to express my indebtedness to the authors.

Obscure as were the diseases of the pancreas a decade ago, and unpromising as was that organ as a subject of general discussion, the situation has within a brief period changed immensely for the better. Indeed, there are few organs in the body which offer a more fertile or satisfactory opportunity of study than the pancreas, and none has received more enlightenment through experimental research. The long interval of sterility extending from the experimental studies of Claude Bernard to those of v. Mering and Minkowski, has been followed by a period of great activity and success in unraveling the physiology and pathology of this gland.

Pancreatitis:—Under this heading I shall consider only the acute forms of pancreatitis, reserving the chronic varieties for the section on diabetes. Acute pancreatitis had been observed by Rockitansky and Klebs and classified by Fitz, who added greatly to the knowledge of the pathological changes and the symptomatology. A satisfactory division of acute pancreatic inflammation into hemorrhagic, gangrenous and suppurative forms can be made. Oser makes a separate form of necrotic pancreatitis, a procedure without clear justification. Necrosis occurs in all forms of the disease and notably in the hemorrhagic variety, although the necroses are sometimes

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small in area. In experimental acute hemorrhagic pancreatitis, which I produced by means of acid injections into the ducts of Wirsung in dogs, necroses were never absent and they varied in size from microscopical foci to areas as large as an almond.

I shall also dismiss the subject of pancreatic hemorrhage with a brief reference. Undoubtedly some cases of so-called pancreatic hemorrhage have been instances of hemorrhagic pancreatitis; but as careful microscopical studies were not carried out this fact escaped detection. For the present we must accept many of the cases of pancreatic hemorrhage reported and admit that so-called pancreatic apoplexy, causing sometimes sudden death, may occur. Spiers described such a condition in 1866, and additional instances have been recorded by Zenker, Prince, Draper and Seitz.

Hemorrhagic Pancreatitis:—The commonest acute form of pancreatitis in man and a form which can be reproduced experimentally in all its anatomical features in animals. It has been admirably described by Fitz, who says, "the gland was found enlarged, either throughout or at one extremity, usually at the head. The gland was frequently doubled in size, and might seem still larger when abundant fat tissue was present. The enlargement has been compared to the size of a man's arm.

"The gland was generally dense, sometimes friable, and has been noticed to be of diminished consistency.

"The existence of hemorrhage was usually suspected by the appearance of the surface, which is of various shades of red. On section, however, the color may be dark red, reddish brown, violet, reddish black, or even black. The modification in color may be uniformly distributed, or lie in patches, or in specks. The patches correspond with nodules which may project above the surface. These discolored patches may show white specks or streaks, and the red color may lie in the interlobular tissue.

"The color of the section may be affected by the presence of associated alterations, one of which is accidental, the other may be incidental. The former is due to an excessive quantity of fat-tissue in the pancreas, sometimes appearing to form nodules as large as hazelnuts and to treble the size of the gland. Bands and spots of a translucent yellow are thus produced, which are mottled with shades of red. The incidental appearance is due to the presence of opaque-white specks, spots, and streaks, which are generally known, since the publication of Balser's article, by the term fat necrosis."

What we know definitely regarding the cause of hemorrhagic

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pancreatitis is due to the attempts at experimental reproduction of the condition. Thiroloix injected several drops of deliquescent zinc chloride into the duct of Wirsung in a dog: the animal died suddenly soon afterwards and the pancreas presented the appearance of a black blood clot. Hlava and Flexner, and later Flexner and Pearce, injected artificial gastric juice into the pancreatic ducts with the result of producing changes in the pancreas indistinguishable from hemorrhagic pancreatitis occurring in man. I was able, also, to show that a considerable number of substances besides gastric juice—formalin, nitric and chromic acids, solutions of caustic alkalies and suspensions of pathogenic bacteria—are capable of provoking in the dog severe, and often rapidly fatal forms of pancreatitis. While the chief variety of pancreatitis met with was the hemorrhagic, running an acutely fatal course and attended with extensive peritoneal fat necrosis, not all the experiments terminated fatally within a brief time. Some animals lived for several days, when the character of the pathological condition might be altered, as, for example, in the sequestration of portions of the injured organ. When death was delayed for several weeks, cysts, abscesses and partial sclerosis of the organ were encountered. In a few instances putrefactive bacteria found an opportunity to develop in the injured organ, when a condition simulating gangrenous pancreatitis in man resulted.

Still other means have been successfully employed to produce acute pancreatitis: Carnot, by the injection of the ferment papaine into the pancreas of a dog caused its death in 25 hours, and found the organ everywhere infiltrated with blood; fat necrosis was absent. The same experimenter produced hemorrhagic pancreatitis by the injection of the diphtheria toxin into the pancreas of a rabbit; and in the same animal similar lesions, causing death in twenty-four hours from injection of a culture of bacillus coli communis.

The most important results are those obtained by Opie from injection of bile into the pancreatic duct of the dog. The injection of 5 cc. of bile into the pancreatic duct caused hemorrhagic inflammation of the gland in four dogs, two of which died within twenty-four hours after the operation. In these experiments death did not follow the use of smaller amounts, and the changes produced in the organ were less widespread and severe. In every case necrosis of the adjacent fat accompanied the lesion of the pancreas, and in two instances in which death occurred spontaneously foci of the necrosis were abundant and disseminated.

The various experimental procedures which have now been used successfully to reproduce the picture of hemorrhagic pancreatitis in

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man, suggests the question as to the probability of any of them operating in causing the natural disease. Three or four possibilities may be considered: first, seeing that the ferment papain can set up inflammation, whether the process can be the result of self-digestion of the pancreas; second, whether bacteria as such are the original injurious agents; third, whether, as Hlava suggested, the gastric juice may be driven by antiperistaltic action of the intestine into the intestine; and fourth, whether bile entering by way of the duct of Wirsung may cause the lesion.

As to the first possibility it may be said that there are no good grounds for invoking self-digestion as a cause of pancreatic inflammation, and the histology of the process is opposed to that explanation; to the second, the variable and inconstant results of bacteriological examination give feeble support to such a view; to the third, that all positive evidence is wanting that gastric juice can be driven into the pancreas, and to the fourth, that many clinical and pathological facts speak in favor of the bile as being concerned with the causation of some cases, at least, of the disease.

Opie has contributed the most convincing data upon the relationship of bile and acute pancreatitis. He says, "The etiology of hemorrhagic inflammation of the pancreas has remained obscure until a series of cases recently studied has demonstrated a relationship between the lesion and cholelithiasis. Since the common bile duct and the duct of Wirsung unite to form the diverticulum of Vater before they reach the duodenum, changes in the one may be transmitted to the other, thus producing secondary lesions of the liver and pancreas. The association of pancreatic disease with alterations of the bile passages has been noted by a number of writers. Körte, in his monograph upon the surgery of the pancreas, mentions the fact that diseases of the bile passages, especially cholelithiasis, are frequently associated with lesions of the pancreas, and it is probable that inflammation can extend from the bile duct to the gland. Oser makes a similar observation, and Lancereaux cites the possibility that a gallstone lodged in the common duct at the level of the diverticulum may occlude the pancreatic duct and produce conditions favorable to penetration of microorganisms into the pancreas."

Opie has collected from the literature the cases of acute pancreatitis associated with cholelithiasis or jaundice and added several additional cases of his own. In one instance the mechanism of the passage of bile into the duct of Wirsung was discovered; and it was the observation of this case that led to the experiments of bile injections into the dog which have been referred to.

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In the human case described by Opie, a gallstone was lodged at the apex of the diverticulum of Vater, blocking the duodenal orifice and connecting the common bile duct and duct of Wirsung into a continuous channel. While, therefore, neither bile nor pancreatic juice were able to pass into the intestine, the two fluids could commingle in the channel, and the direction of the flow, whether upward towards the liver or across into the pancreas, would be determined by the relative pressure in the two ducts. "The pressure at which bile and pancreatic juice are secreted being small, any slight difference that might exist would be overcome by the gall bladder, a muscular organ which at intervals forces bile in considerable quantity along the common duct." That bile actually passed along the pancreatic duct into the pancreas in this case was shown by the bile staining of the duct and the histological examination of the inflamed organ.

It would, therefore, seem as if in the entrance of bile into the pancreatic duct a sufficient cause of many cases of hemorrhagic pancreatitis has been found. The close agreement of the lesions in the human case with those of experimental bile injections into the pancreas in dogs, lends further support to this manner of production of the natural disease.

The question of the precedence and succession of hemorrhage and necrosis and the inflammatory phenomena has been mooted. Katz and Winkler consider that the necrosis of the tissue follows hemorrhage and is the direct result of the injury done by the extravasated blood; Hlava looks upon the extensive occlusion of blood vessels, which followed his acid injections, as the primary cause both of the hemorrhage and necrosis; and Opie finds the association of injury of parenchyma and of adjacent vessels to be so intimate that while necrosis occurs in the one extravasation takes place from the other. My earlier experiments showed that extensive hemorrhage may precede necrosis of pancreatic tissue, be associated with necrosis, and be independent of gross or microscopic closure by thrombi of blood vessels; from which I drew the conclusion that hemorrhage and necrosis are both the results of simultaneous action of the injurious agent upon blood vessels and upon tissue; that they occur coincidentally, and, according to various circumstances attending the action, sometimes necrosis will occur independently of hemorrhage and *vice versa.*

To determine the action of sterile blood upon the pancreas, injections were made by Dr. Pearce and myself into the organ through the pancreatic duct and directly into the parenchyma. Such injec-

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tions do not suffice to set up acute pancreatitis, but they are followed by decolorization and disappearance of the red corpuscles from the organ and the occurrence of proliferative activity of the connective tissue in and about the acini. This proliferative process, affecting a part only of the organ, quickly gives rise to new growth of tissue, which takes the place of the glandular acini and islands of Langerhans.

The rapidity with which serious symptoms arise in acute pancreatitis led Dr. Pearce and me to study the development of the inflammatory process in the pancreas after acid injections. This was accomplished by removal, from time to time, of portions of the gland which were subjected to histological examination. A brief resumé of the results are appended:

At the end of one hour, after intraduct injections, the pancreas is already considerably affected. The first effect is, of course, the distention of the ducts with the injected fluid, but direct injury to the lining epithelium of the larger ducts does not appear; from here the fluid flows backward into the smaller inter- and intra-acinous ducts, which show colloid material filling their lumina, although the epithelium still stains distinctly. From the ducts the fluid seems to pass only to a slight extent directly into the acini themselves, but rather through the walls of the ducts into the pericanalicular and interlobular connective tissues. In these locations an albuminous and fibrinogenous fluid has exuded and undergone coagulation and precipitation. One of the striking effects is the widespread distention of the capillaries and the alteration in form of the red corpuscles. The inter-acinous capillaries and capillaries of the island of Langerhans are turgidly swollen and the red blood corpuscles are in *rouleaux*. Among these, white cells are not especially abundant, but inter- and intra-acinous, microscopical hemorrhages have already taken place. The medium-sized, interacinous veins show distention, red corpuscles *in rouleaux and increase in polymorphonuclear cells.* The white cells in occasional veins form plugs, which do not, however, completely occlude the vessel, for an active emigration is going on. Leukocytes can be seen making their way through the walls and entering the adjacent tissue. Even red corpuscles can be seen engaged in the unruptured vessel walls, as well as just outside. There are no vascular thrombi. The parenchymatous cells already show distinct changes. Not many cells are affected, but occasional islands of acinous cells are *partially or completely hyaline.* The nuclei are still weakly stainable, but the protoplasm is swollen and

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homogeneous, and *polymorphonuclear cells have begun to approach these areas or have actually entered the altered protoplasm.* The largest hemorrhages, quite visible to the naked eye in sections, are in the interlobular tissue and about the larger veins, which latter show *leukocytic wandering and diapedesis through unruptured wall.*

Seventy minutes after injection the changes are more marked: the degeneration of the parenchymatous cells is far in advance of the other. The distribution of the degeneration is interesting as indicating the manner of diffusion of the injection. The hyaline cells are often the outermost layer, next the interlobular connective tissue. Large, degenerated foci (consisting of one or more acini) are also present. Leukocytic emigration, as would be expected, on account of the greater degree of degeneration, is a marked feature, and gives rise to small islands among the necrotic cells. There are many leukocytes in the interstitial edema. After eighty minutes this interstitial cellular accumulation begins to approach purulent infiltration. At the end of two hours and fifty minutes the process has gained some in intensity.

A specimen taken four hours after the injection shows still further advance. The edema is extreme and has isolated certain lobules, the cells, however, still staining sharply. But the necroses are very large and numerous and the nuclear changes are striking.

After the elapse of five and one-half hours the most important new phenomenon is the appearance of large numbers of large, mononuclear cells in the interstitial tissue, chiefly about the veins, mingled with red corpuscles and polymorphonuclear cells. The necrotic and degenerated cells begin to separate from one another, some assuming circular forms, and coincidentally the leukocytic infiltration (chiefly polymorpho- and slightly mono-nuclear) is so greatly increased as to approach the appearance of an abscess. Parietal thrombi are to be made out in some medium-sized veins. Hemorrhage has increased considerably and elevates the capsule of the gland.

The final specimens of this series are eight hours old. They represent the pathological process at its height. To what has already been stated there need only be added the coincidence of hyaline necrosis and hemorrhage, and the free hemorrhage in other parts causing complete disorganization of the acinous structures. The capsule of the gland is covered with a fibrino-purulent hemorrhagic pseudo-membrane.

The peritoneal fat necroses are typical, and about them a well-advanced cellular accumulation may be noted. While there is no

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record of fat necroses occurring so quickly as in this instance, I have little doubt but that they may make their appearance even earlier than eight hours after injury to the pancreas. Especial attention had not been directed to the elucidation of this question.

This series of experiments has a general as well as special interest. The rapidity with which morphological changes in cells may be made out, and the celerity with which emigrative phenomena is vessels take place in warm-blooded animals is well illustrated by these examples. That degenerative, inflammatory and hemorrhagic lesions are correlated in the pancreas may now be considered as demonstrated. There need be no time interval, or no considerable one, between the appearance of the several phenomena.

Gangrenous Pancreatitis:—Fitz has given the classical description of this condition, and he recognized the association of hemorrhagic inflammation of the pancreas with gangrene. The series of events are described by him as follows: The gland is at first swollen, dark red, and soft, while on section the tissue is red or mottled red and gray, or, maybe, wholly transformed into a dark, slate-colored, foul-smelling mass. At the end of about ten days the pancreas is often dark brown, dry and firm, and covered by changed blood, and the hemorrhagic infiltration may extend beyond its limits. Throughout the substance areas of hemorrhage alternate with yellow spots of softening. At the end of the second week the organ may form a soft, black, friable mass, while the lesser omental cavity contains a large quantity of chocolate-colored fluid containing bluish black clots. The gland may be finally transformed into a soft mass attached by a few shreds to the posterior abdominal wall, or, indeed, may lie free in the omental cavity, which is distended with bloody or blackish, often ill-smelling, fluid containing necrotic particles of tissue. Fat necrosis of the intraabdominal fatty tissue occurs.

Fitz correctly reached the conclusion that in a considerable number of cases of gangrenous pancreatitis there was associated hemorrhagic inflammation of the gland, but he also recognized the possibility of origin of the lesion from perforating inflammation of the gastro-intestinal or biliary passages.

The series of transformations through which the diseased gland passes leaves little doubt that in the majority of instances the primary lesions are inflammation with necrosis and hemorrhage, and the putrefactive changes are secondary and incidental and arise from invasion of the dead and injured tissues by putrefactive micro-organisms from the intestinal canal. In two of the experiments

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which I carried out in dogs the hemorrhagic and inflamed pancreas was invaded by putrefactive bacteria and gangrene of the organ resulted.

Opie's table, moreover, shows that of twenty-one case of acute pancreatitis associated with cholelithiasis eight are described as hemorrhagic and gangrenous and thirteen as gangrenous.

Suppurative Pancreatitis:—Two varieties of this condition are distinguished: primary and secondary. The former variety originates in the pancreas, the latter proceeds from a neighboring organ or arises through metastasis. In both varieties the abscesses may be single or multiple.

The relation which the pancreas bears to the lumen of the intestine and to the hollow abdominal viscera exposes it to bacterial invasion through its ducts or directly from ruptures and perforations of these organs; while pyogenic bacteria may be brought to the pancreas by the general blood current or ascend into it from thrombotic infections of the portal system of veins. Previous injury, especially such injury as leads to necrosis of the pancreas, predisposes the organ to suppuration. While the abscesses usually involve a fraction only of the pancreatic tissue, yet the whole gland may undergo degeneration and come to lie as a sequestrum in a pus cavity. As illustrating the possible manner of formation of circumscribed abscesses with necrosis of the pancreas in man, the following experiments carried out on dogs are given:

June 9. Medium-sized dog. 5 cc. of 1 per cent. HCl were injected into the duct. The animal was killed July 5. The local wound had healed; the peritoneum was normal; the pancreas in the neighborhood of the spleen was swollen and contained in its center a grayish brown slough the size of a pea; the surrounding tissue was indurated. No fat necrosis was noted.

June 8. Small dog. 4 cc. of 2 per cent. HCl were injected into the duct. The pancreas immediately afterward assumed a yellowish green tinge in its duodenal part. The animal was chloroformed July 5. Autopsy. The duodenal end of the pancreas is swollen, indurated and included in adhesions of the omentum, duodenum, etc. On section a small central cavity, containing glutinous material, gray in color, is disclosed. No necrotic pancreatic tissue exists elsewhere, but several whitish areas, which resemble necroses, occur in the fibrous indurated pancreatic tissue.

June 24. Large dog. 3 cc. of 1 per cent. H_2SO_4 were injected intraparenchymatously. The animal was chloroformed July 5. The

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local wound had healed. There are adhesions about the left end of the pancreas, where the organ is much swollen. On removing the adhesions, a small quantity of gelatinous, gray, puriform material escapes, leaving behind a cavity about the size of a chestnut, in which there is a sequestrum. New tissue seems to be forming in other portions of the organ, which are indurated. No fat necroses are noted.

June 22. 4 cc. of 2 per cent. HNO_3 were injected into the duct. The animal died June 24. The peritonium contains a small amount of turbid bloody fluid, and the serosa is greatly injected. The pancreas is greatly swollen and hemorrhagic; the hemorrhagic areas are irregularly distributed and give a mottled appearance to the organ, which is covered with a pseudo-membrane. The pancreas, on section, shows grayish areas of necroses, surrounded by pancreatic tissue infiltrated with blood. About the pancreas there are several accumulations of pus. Fat necroses exist in the omentum and in the lesser curvature of the stomach.

January 26. 5 cc. of 1 per cent. NaOH were injected into the duct. Discoloration and a collection of fluid in the interstitial tissue followed immediately. The animal was chloroformed February 9. In the peritoneal cavity there is a small amount of slightly blood-stained fluid; the serosa is bright. About the middle and transverse portions of the pancreas, there are dense adhesions, which include the duodenum, stomach and omentum. On dissecting away these parts, an abscess the size of a walnut, filled with thick, creamy pus, is exposed. It is surrounded by thick, fibrous walls and does not contain pancreatic tissue. The descending portion of the pancreas is pale in color. No fat necroses are present.

February 9. Small dog. 4 cc. of faintly turbid suspension of B. pyocyaneus were injected into the duct. The animal died February 11. The external wound is perfect. The peritoneal cavity is slightly moist, the surface of the serosa being turbid, the omentum well spread out. No fat necroses are seen in it or in the mesenteric fat. The duodenum in its second portion is closely applied to the body of the pancreas, which, in its mid-portion, is swollen to a great degree and measures 4 cm. in thickness. The organ is dark in color and hemorrhagic, and a central area of softening, measuring 2 x 2 cm., is noted. The surrounding pancreatic tissue is infiltrated with blood, and is opaque in color, the lobulations being very indistinct. The rest of the pancreas is pale. No fat necroses are seen. Cultures from the peritoneal cavity and from the softened area in the pancreas are positive for B. pyocyaneus.

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A study of the histology of the pancreas in experimental pancreatitis led me to the following description of the suppurative inflammations produced in the dog:

"The typical examples of suppurative pancreatitis are associated, not with diffuse infiltration of the tissue with pus cells, but with focal accumulations of pus cells in the form of abscesses. These abscesses may be chiefly limited to the larger masses of interstitial tissue; whence the pus cells may pass along the smaller septa, eventually arriving between the acini. In other cases the collections may be chiefly in the parenchyma. The two forms, the suppurative and the necrotizing pancreatitis, may co-exist, and it happens also that scattered hemorrhages may be present in sufficiently large numbers, and be of a size that will give a hemorrhagic character to the former form of pancreatitis. But although the hemorrhages may be abundant, it should be borne in mind that in a pure hemorrhagic pancreatitis, focal accumulations of pus cells, in the form of abscesses, do not occur."

In one example of suppurative pancreatitis, hemorrhages, even of a large size, were numerous in the interstitial tissue, while necrosis, occurring especially in the centers of the lobules, were also common. These necroses were surrounded with living pancreatic tissue, and suggested a very direct action upon the central portions of the lobules, due to the injurious material introduced through the ducts.

Diabetes:—In the year 1788 Cowley published a carefully studied case of severe diabetes with pancreatic calculus and atrophy of the gland. Other reports, of a later date, were made by Chopart, Bright, Lloyd, and Elliotson. Bouchardat (1851) would seem to have been the first writer to have connected definitely disease of the pancreas with diabetes. Lancereaux (1877) drew especial attention to this relation. He was followed by Lapierre (1879) and Baumel (1882); but since that time the literature on this subject has grown rapidly.

The experimental contributions to the functions of the pancreas, except so far as its intestinal secretion is concerned, had yielded no remarkable results until von Mering and Minkowski's publication on the effects of complete extirpation of the gland in the dog (1889), although Haller had already stated that it was followed by increased hunger and thirst. Claude Bernard showed that tying off the duct of Wirsung produced no effect, and Schiff, who injected fat into the ducts, saw the gland atrophy, but apparently without causing diabetes.

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Extirpation of the pancreas in the dog causes, without exception, diabetes of severe grade. As this aspect of the subject under consideration by the Congress will be dealt with by another speaker, I will not consider it further at this time.

There are no records of complete removal of the pancreas in human beings. Partial resections of the gland have been followed by glycosuria (Zweifel) or diabetes (Hahn, Korte, Krönig, and Bull). In the latter cases the interval between the operation and appearance of the symptoms was as great as one and three-fourths years, and the result may have depended upon a progressive degeneration. That the pancreas in human beings shows marked pathologic changes in cases of diabetes is shown by numerous observations. Windle examined the pancreas in 139 cases of diabetes, and found it normal in only 65; Frerichs found it normal twenty-eight times and atrophic twelve times in 40 cases of disease. Seegen found among 92 cases of diabetes autopsied at the Vienna Pathological Institute, 17 in which there was pancreatic disease. Dieckhoff examined 19 cases of disease of the pancreas, and of these patients 7 were diabetic. Hansemann found among the protocols of the Berlin Pathological Institute, tabulated for ten years, 8 cases of diabetes without pancreatic disease, 6 cases in which no reference is made to the condition of the pancreas; 40 cases in which pancreatic disease and diabetes were associated, and 19 cases in which there was pancreatic disease without diabetes. The 40 cases of pancreatic disease and diabetes consisted of 36 instances of simple atrophy, 3 of fibrous induration, and 1 of a complex nature. Hale White found, in the autopsy records of Guy's Hospital (1883-94), 99 examples of disease of the pancreas. Of these, 16 were instances of atrophy, in 13 of which diabetes had existed. Naunyn, on the other hand, in 40 autopsies on cases of diabetes, saw only 1 in which he considered the pancreas to be the cause of the disease.

Of the causes of the pathologic changes in the pancreas which produce diabetes, the chief one is supplied by concrements in the ducts. Of the 72 cases in the bibliography, 14 were due to pancreatic calculi (Hansemann). Naunyn's case was of this nature. The pancreatic changes consist of secondary atrophy. Next in frequency come the primary atrophies, fibrous indurations, and instances of interstitial lipomatosis. Attention should be paid to another possible explanation of pancreatic atrophy—namely, a cachetic condition which may be the result and not the cause of diabetes (Friedreich, Naunyn). Hansemann has undertaken to dis-

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tinguish between the two forms of pancreatic atrophy. In the cachetic form the organ is cylindric and sharply demarcated from its surroundings. Microscopically, the stroma and glandular cells are uniformly atrophic. In diabetic atrophy there is interstitial pancreatitis; on account of adhesions the gland is with difficulty separated from its surroundings and presents a brownish coloration (although it is not pigmented), is of a smoother texture, and microscopically shows hypertrophy of the stroma and atrophy of the secreting cells. But that such examples of interstitial pancreatitis need not invariably be associated with diabetes, the two cases of Obici prove. Hansemann has seen diabetes in an early case of interstitial pancreatitis, and is of the belief that a particular form of pancreatitis, which he calls granular atrophy, is always associated with diabetes. Hanot has described cases of bronzed diabetes (*diabète bronzé*) in which, besides pancreatic disease, hypertrophic cirrhosis of the liver has been presented. Twenty-four cases of the disease, all in males, have been collected by Anschütz. Opie has examined the pancreas from 19 cases of diabetes and noted the condition of the various histological elements of the gland. The following lesions were discovered: in one case chronic interlobular pancreatitis with calculi; in three cases chronic interacinar pancreatitis; in seven cases hyaline degeneration of the islands of Langerhans with, in some instances, chronic interacinar pancreatitis; in four cases the pancreas was atrophied, and in four no pathological condition was found.

Opie does not agree with those writers who look upon duct obstruction as the most common cause of pancreatic sclerosis leading to diabetes. On the other hand, he finds chronic pancreatitis, due to other causes, not infrequently associated with diabetes, although chronic pancreatitis is not always, or, indeed, in the majority of instances, accompanied by diabetes.

Various observers have attempted to define a type of pancreatitis pecliar to diabetes: as the arterial-sclerotic interstitial inflammation of G. Hoppe-Seyler and Fleiner, and the perivascular sclerosis of Lemoine and Lannois. Associated with the latter is a penetration of the fibrous strands into the acini, separating the cells and producing what they denominate uincellular sclerosis. Hansemann's atrophy of the pancreas is claimed by him to be constantly associated with diabetes, but it is not always easy to separate the condition from that which he distinguishes as atrophy consequent upon emaciation. In the former there is an evident overgrowth of the interstitial tissue;

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in the latter both glandular and interstitial elements have suffered diminution.

Opie has laid emphasis upon two varieties of chronic inflammation of the pancreas: (1) interlobular pancreatitis, characterized by proliferation of fibrous tissue between the lobules which are invaded from the periphery and (2) interacinar pancreatitis, in which the newly-formed fibrous tissue is more diffusely distributed within the lobules and between individual acini. With the first type the islands of Langerhans are implicated only when the sclerotic process has reached a very advanced grade. To this variety, he states, belongs the chronic inflammation which follows occlusion of the pancreatic ducts. With the interacinar type of inflammation the islands are affected as are other elements of the gland, and coarse strands of fibrous stroma following the capillary vessels separate columns of atrophied cells.

Of twenty-one instances of chronic pancreatitis of the interlobular type Opie found diabetes present in only one. In this instance the sclerosis had reached a very advanced grade, and the islands of Langerhans, isolated in the dense stroma, had undergone alterations. In seven of nine instances of interacinar pancreatitis, diabetes mellitus was present. In one case without diabetes the lesion was but little advanced.

It is evident from the above account that Opie looks upon the implication of the islands of Langerhans in the inflammatory process to be the crucial fact in determining the occurrence of diabetes. He finds support for this view, which implies the exercise of control by these structures over carbohydrate metabolism, in a series of cases of diabetes in which the chief lesion in the pancreas was a hyaline transformation of the cells, including sometimes, the capillaries of the islands.

As illustrating the surprising frequency with which selective lesions affecting the islands of Langerhans and accompanied by diabetes occur, Opie states that in six of the nineteen cases of diabetes which he studied they have been found. Since his publications confirmatory observations have been recorded by Weichselbaum and Stangl, Gentes, Wright and Joslin, Herzog and Schmidt.

There is little doubt that our knowledge of pancreatic diabetes has been extended in a most important manner by the studies of Opie and his followers.

Before concluding this topic I wish to speak briefly of the production in two dogs of a marked grade of interstitial overgrowth of con-

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nective tissue by injecting large quantities of sterile, comminuted pancreas into the peritoneal cavity. Several injections averaging one-third to one-half of a pancreas were borne. On killing these animals after some weeks a moderate general thickening of the peritoneum was present, most marked over the liver. The pancreas was markedly firmer than normal, and on microscopical section showed increase in interstitial tissue of a cellular type. The liver of one dog also showed an overgrowth of interlobular tissue which grew into the organ from the capsule. In other dogs treated in the same way the lesion failed to appear.

Fat Necrosis:—It is customary to date our knowledge of this condition from the epoch-making observations of Balser, made in 1882 although in the older literature the condition is referred to in unmistakable terms. Thus, Schmidt in 1818, Rokitansky in 1844, Virchow in 1852, Klob in 1860, Hooper in 1861, Klebs in 1870 and Ponfick in 1872, all described undoubted examples of fat necrosis.

Balser's description, which is based upon his observations of five instances of fat necrosis, which he collected from the autopsy material in Breslau, is classical. He says that one finds frequently in adults, who may be emaciated or well nourished, in the interacinous tissues of the pancreas and stomach, much more rarely in the surrounding adipose tissue, whitish foci, varying in size from a pin point to a pea, which often present an opaque, yellowish white tint. In rare instances these areas increase in number and in size, while at the same time they undergo a central form of necrosis, with which may be associated either fresh or old hemorrhages that extend into the surrounding tissues. The necroses may become confluent, and a demarcating inflammation may ensue with the production of sequestration. Similar yellowish white foci have been found in the adipose tissue of the medulla of bones and of the heart. These appearances were referred by Balser to the presence of bacteria, although, as he confesses, the micro-organisms could not be demonstrated upon microscopical examination. In spite, however, of this important flaw in the evidence, Balser considered it probable that, as in the case of tuberculosis, certain organisms had caused proliferation of the fatty cells, and that these had as a result eventually undergone degeneration and necrosis.

That bacteria may be associated with fat necrosis had previously been pointed out by Ponfick, when describing a lesion in the long bones of a young woman of twenty-one, who had suffered from empyema, amyloid degeneration, etc., and in whose heart muscle

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disseminated necrotic areas were also demonstrated. But although it cannot be denied that bacteria may be present, on the other hand, their relation to the lesions of fat necrosis would seem to have been strikingly irregular, and thus far experimental attempts to produce such areas by injections of bacterial cultures have failed. The micro-organisms which have been isolated are the usual pyogenic cocci (Jackson and Ernst, Hlava, Lubarsch), the bacillus coli communis (Welch, Ponfick, Hlava) and certain unidentified species, which in all probability have entered from the intestine. As Welch has pointed out, in discussing the presence of B. coli communis in one case, the combination was probably the result of a general infection with that micro-organism, which, however, could not be considered as the cause of the local pathological condition. To these observations I can add, from the bacteriological study of a case of disseminated fat necrosis in a woman, the isolation of two organisms. One of these agreed with B. coli communis; the other, while showing the same morphology, failed to ferment any of the sugars, and its identification was, therefore, left in doubt.

Injections of micro-organisms directly into the substance of the pancreas, which have in some instances been found to give rise to slight fat necrosis, will be referred to later on, when reference is made to the effects which these injections produce upon the pancreas in causing inflammation of that organ, with which the fat necrosis has been associated.

The first experimental proof of the relation of fat necrosis to the pancreas was brought by Langerhans, who injected suspension of pancreas (comminuted with glass in order to separate the ferment and then filtered) into the perirenal fat of rabbits and dogs; in one instance he obtained evidence of necrosis. From this successful experiment the conclusion was drawn, that the lesion was produced by direct action of the fat-splitting ferment contained within the pancreatic secretion upon the fat contained with the adipose tissue cells.

The subsequent studies of Hildebrand, Dettmer, Milisch, Körte, and in this country of Whitney, Williams, Opie and the writer, have brought indubitable proof of the relation between the pancreas and fat necrosis. In the experiments carried on by these workers the ducts of the pancreas were tied off so as to produce an escape of the secretion into the lymphatics and into the peritoneal tissues; or, in other instances, the organ was lacerated, ligated or in other ways injured with the object of allowing the pancreatic secretion to flow into the abdominal cavity. That fat necrosis can be produced by

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these several means has been abundantly proven, and that the necroses owe their origin to the presence of the fat-splitting ferment has been shown by the writer upon the basis of chemical tests.

That fat necrosis depends upon the action of the pancreatic secretion is still further proven by those experiments in which portions of the pancreas have been transplanted to the peritoneal cavity of healthy animals, or brought into contact with the fat of the subcutaneous tissues (Williams, Opie); and by stimulating the secretion of the pancreas, after ligation of its ducts, as performed by Opie by means of pilocarpin injection, in which event widespread necroses occur much more quickly.

The observations of Ponfick, Balser and Chiari of the occurrence of necroses in the pericardium and in the medulla of bones suggested a possible bacterial action. But I have found the necroses in the pericardial and subcutaneous fats, following acid and other injections into the pancreas, and from which bacteria could with certainty be excluded; and Opie has described similar and even more intense widespread lesions after ligation of the pancreatic ducts and pilocarpin injections in cats. It may, therefore, be taken as demonstrated that para-pancreatic as peri-pancreatic fat necrosis is produced by the action of the fat-splitting ferments of the pancreas, and that the manner of action of bacterial injections into the pancreas, with which such necroses have sometimes been associated, is merely to open the way for the escape of the pancreatic secretion into tissues.

Wells has come to interesting, though not unexpected, conclusions upon the experimental production of fat necrosis, which he induced by means of commercial "pancreatins" and other means. He found that the power of pancreatin to produce that special form of necrosis survived heating for five minutes at some point between 65° and 71° C., although the amount of necrosis steadily decreased after exposure to 55° C. and upwards, facts which, as he observes, point to enzyme action as the source of the lesion.

Wells found it impossible to ascertain which of the pancreatic enzymes causes fat necrosis. Trypsin, weak in or devoid of lipase, does not produce it; lipolytic extracts of hog's liver or cat's serum fail likewise, and mixtures of lipolytic extracts of liver with pancreatic trypsin are also ineffective. If to such extracts as the last an emulsion of duodenal mucosa is added, the tryptic activity is greatly enhanced but necrosis fails utterly to appear. As the lipase of pancreatic extract cannot be isolated it is impossible to experiment with it alone. Wells suggests that perhaps it is only after some other

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ingredient of the pancreatic juice has injured the fat cell that the lipase splits the fat molecule; and he has, moreover, confirmed the supposition that the lipase normally in fat tissue is incapable of splitting the fat, when the fat is rendered necrotic and preserved from external influences.

Fat necrosis in human beings receives an adequate explanation on the basis of its successful experimental production, and the observation of the conditions under which many cases in man have occurred. The prime requisite is the escape of pancreatic juice into the peri- and para-pancreatic adipose tissue. This escape is permitted by acute destructive lesions of the pancreas and also by obstructions, either temporary or permanently, of the pancreatic ducts. The literature contains a number of examples in which these conditions were fulfilled, and the association of biliary concrements and fat necrosis has especially been noted. I reported some years ago the case of a woman of 50 years in whom death occurred suddenly, the abdominal fat being studded with necroses, in whom, in the common bile duct near its termination, gallstones were present. In this case and in cases of similar nature a temporary obstruction of the duct of Wirsung may be presumed, the retained pancreatic secretion passing into tissues about the pancreas and being transported, possibly, by the lymphatic current to a distance.

The not infrequent association of fat necrosis and chronic interstitial pancreatitis admits, as Opie has pointed out, of a similar explanation. Even in the absence of constriction by fibrous bands of the large ducts, the smaller ones may be pressed upon, producing local obstruction to the outflow of the secretion, and its diffusion into surrounding tissues.

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THE PANCREAS AND PANCREATIC DISEASES.

THE SYMPTOMATOLOGY AND DIAGNOSIS OF DISEASES OF THE PANCREAS.*

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The consideration of the symptomatology and diagnosis of diseases of the pancreas may appropriately be introduced by referring to the memorable communication on this subject by Friedreich (von Ziemssen's *Handb. d. Sp. Path. u. Therapie.*, 1875, VIII, 2, p. 234), nearly thirty years ago. According to this authority "no single symptom which may occur in diseases of the pancreas is pathognomonic and the concurrence of several does not always result in a positive diagnosis. . . . . Fatty stools, mellituria, epigastric pains with the characteristics of caeliac neuralgia, and a palpable tumor lead among the symptoms most useful in diagnosis" and (p. 223) the presence of undigested, striated muscle-fibres in the faeces "is worthy of every consideration and may, perhaps, prove of diagnostic value."

For a while no material additions were made to the clinical pathology of the pancreas, but in 1887 the investigations of Müller (*Ztschr. f. klin. Med.*, 1887, XII, 45), and especially those of v. Mering and Minkowski (*Arch. f. exper. Path. u. Pharmakol.*, 1889, XXVI, 371) in 1889, excited a renewal of interest in the matter. Since then physiologists and pathologists, physicians and surgeons in various parts of the world have made numerous contributions to the knowledge of the functions and lesions of the pancreas, and this gland has become recognized as of the greatest importance in maintaining and promoting a healthy state of the body. Within the past five years have appeared the notable treatises of Körte, Oser, and, more recently, that of Mayo Robson and Moynihan. These are the authors now to be consulted for classified knowledge of the questions under consideration. From them is to be learned in what respects the clinical characteristics of pancreatic diseases are now more sharply defined than in the days of Friedreich and his predecessors.

It is generally agreed that the symptoms especially suggestive of

* The writer wishes to acknowledge his indebtedness to Dr. J. H. Pratt, of Boston, for assistance in reviewing the literature of the subject.

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pancreatic disease are dependent largely upon the resulting disturbances of its functions and upon the situation of the organ. The former include the various modifications in the composition of the urine and faeces; the latter comprise the localized resistance, tenderness and pain, and the evidence of obstruction of the gastro-intestinal and biliary tracts. Unfortunately for diagnostic purposes, the functions of the pancreas are not the exclusive property of this gland, but are possessed to a greater or less extent by other structures and other agencies.

For more than a century it has been known that diabetes may be associated with disease of the pancreas. More than eighty years ago visible faecal fat was found to hold a like relation. Forty years later the presence of undigested muscle-fibres in the faeces first attracted attention. These observations have since been repeated with sufficient frequency to lead the physician to suspect, often to assert, the presence of disease of the pancreas when one or more of these conditions have been determined. The comparison, however, of the results of anatomical investigation with clinical observation makes it evident that diseases of the pancreas much more frequently occur without the recognition of glycosuria, and of fat and muscle in the faeces than when these abnormalities are apparent.

The physician, therefore, wishes to know if one or more of these conditions are present in some diseases of the pancreas, why are they not present in all? If found in a certain instance of a single variety, why are they not present in all or in most of the cases of this particular affection? Morbid changes of the pancreas are found frequently after death without symptoms having been observed during life to indicate their presence. On the other hand, the diagnosis of probable pancreatic disease, perhaps of the gravest sort, has been made from the recognition of one or more of the symptoms or signs which, at times, have been found associated with alterations of the pancreas and the patient has recovered or the gland when exposed has presented no abnormal appearance.

From the data collected by Oser it is evident that the symptoms attributable to disturbed pancreatic function are almost invariably connected with chronic lesions productive of extensive destruction of pancreatic tissue or with interference to the passage of its secretion into the intestine. The pancreatic lesions usually associated with diabetes are those in which the common element of interstitial inflammation exists with a corresponding destruction of the parenchyma of the gland. This may occur in the form of the genuine,

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granular atrophy of Hansemann, in calculous pancreatitis, or in the sequence of chronic suppuration, cysts and tumors.

Visible faecal fat and azotorrhoea, on the contrary, are oftener associated with chronic conditions interfering with the flow of pancreatic juice into the intestine as obstruction of the ducts from calculi, stricture or tumors, than with those causing destruction of the secreting cells of the gland. Rarest of all is the presence of alterations which are associated with diabetes, and fat and numerous muscle-fibres in the faeces. The case reported by Fles (Friedreich, op. cit., 222) is almost unique in these respects. His diabetic patient ate much bacon and fat meat and evacuated so much unabsorbed fat that it could be scooped by the ounce from the faeces. The latter contained also large numbers of undigested, striated muscle-fibres. The autopsy showed that the pancreas was represented only by fragments of the fibrous framework and scarcely recognizable traces of the gland substance. The duct could not be found. Nevertheless, it is evident from human pathology that extensive destruction of the pancreas may take place without observable modification of function. Franke (*Arch. f. klin. Chir.*, 1901, LXIV, 364) extirpated a cancerous pancreas and, although the patient lived five months after the operation, there was glycosuria merely for a few days and the stools appeared normal. The patient of Trafoyer (Chiari, *Wiener med. Wchnschr.*, 1880, XXX, 139) was well seventeen years after a pancreatic slough was discharged from the bowel.

The inference from such observations is that in extensive destruction of the pancreas without obvious disturbance of function, enough of the gland is left intact, or an accessory pancreas or other organs or agencies are present to assume the pancreatic functions. Even when the pancreas presents an apparent integrity and fatal diabetes exists, the researches of Ssobolew (*Centralbl. f. allg. Path. u. Path. Anat.*, 1900, XI, 202) and Opie (*Jour. Boston Soc. Med. Sci.*, 1900, IV, 251) make it evident that destruction of the islands of Langerhans may have taken place. Their investigations and those of other observers directed to this possibility add force to the suggestion that in the destruction of these islands may lie the important factor in explanation of diabetes in certain of the cases in which the gross appearance of the pancreas are normal. Hence, with the recognition of various causes of glycosauria and diabetes, these affections, in the light of our present knowledge, are attributable to disease of the pancreas only in those instances in which there

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is extensive degeneration or destruction, either limited to these islands or affecting also the parenchyma of the gland.

If the diabetes is associated with long continued bronzing of the skin and enlargement of the liver, in the absence of jaundice and the characteristic distribution of the pigment in Addison's Disease, the suggestion is direct that chronic, fibrous pancreatitis is present. Since the original publication by Hanot and Chauffard (*Rev. de Med.*, 1882, II, 385) on this subject, the bronzed diabetes of French writers, Anschutz (*Deutsch. Arch. f. Klin. Med.*, 1899, lxii), has tabulated twenty-four cases of this combination. The view that the affection of the pancreas is the remote result of the deposition of the pigment in the haemochromatosis of v. Recklinghausen has repeatedly been favored by recent writers (Oser. Nothnagel's *Encyclopaedia, Am. Edition*, 1903, 737).

Steatorrhoea is next in importance to glycosuria and diabetes as evidence of disturbance of pancreatic function although the views concerning its insignificance are somewhat divergent. The presence of oil readily attracted attention, but it soon became apparent that the fat might assume a solid as well as a liquid form. It was considered that the presence of fat represented an increase of this constituent the absorption of which was interfered with in consequence of the disease of the pancreas. Müller (*loc. cit.*), however, called attention to the frequent concurrence of disturbance of biliary secretion in the cases reported. He emphasized the importance of a lack of bile in the intestine as interfering with the absorption of fat and considered it doubtful if a lack of pancreatic juice could cause steatorrhoea. He endeavored to show that a deficiency of split fat, the proportion of total faecal fat being normal, was the chief feature when there was lack of the pancreatic juice and that interference with the flow of bile was the main cause of pathological steatorrhoea. Müller reported but three cases of pancreatic disease in support of his views. Jaundice was present in one only. In another the actual condition of the pancreas and its duct was not to be determined as the patient was seen after having been operated upon for "cyst" of the pancreas.

In order to obtain further clinical evidence on this point, a table has been prepared to show the relation between visible faecal fat, jaundice and pancreatic disease. Only those cases are included which gave anatomical evidence at an autopsy, a laparotomy, or by the passage of a pancreatic calculus that there was actual disease of the gland.

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I.—Relation of Fatty Stools in Pancreatic Disease to Diabetes or Glycosuria and to Jaundice.

	Lesion.	Stools.	Diabetes or Glycosuria.	Jaundice.	Authority.
1	Fibroadenoma	Fatty	Present	Present	Biondi, Oser, op. cit.
2	Cancer	Fatty	Absent	Present	Bowditch, Boston M. & St. J., 1872, LXXXVII, 65.
3	Cancer	Like butter	Absent	Absent	Bright. Med. Chir. Trans., 1833, XVIII, 1.
4	Cancer	Like butter	Present	Present	Bright. Med. Chir. Trans., 1833, XVIII, 1.
5	"Cyst"	Free fat	Present	Temporary	Bull, N. Y. Med. J., 1887, 376.
6	Calculi	Fatty	Absent	Absent	Capparelli, Oser, op. cit.
7	Calculi	Fatty	Absent	Absent	Chopart, Oser, op. cit.
8	Calculus passed	Fatty diarrhœa	Present	Absent	Cipriani, Therap. Monatsh, 1898, XII, 617.
9	Cancer	Like butter	Absent	Absent	Clark, Lancet, 1851, II, 152.
10	Atrophy, cong. syphilis	Like asbestos	Absent	Absent	Demme, Oser, op. cit.
11	Calculus	Oily, at times like butter	Present	Absent	Elliotson, Med. Chir. Trans., 1833, XVIII, 77.
12	"Cyst"; atrophy, fibrous tissue in head of pancreas	Masses of fat crystals, once consistency of sweet oil	Present	Absent	Goodman, Tr. Path. Soc., Phila., 1878, VIII, 41.
13	Indurated pancreas, obliterated duct	Fatty	Absent	Present	Kuntzmann, Friedreich, op. cit.
14	Cancer	Fatty	Absent	Absent	Labadie-Lagrave, Oser, op. cit.
15	Calculus. Atrophy. Growth of fibrous and fat tissue	Fatty before onset of diabetes.	Present	Absent	Lancereaux, Bull. Acad. de Med., 1888, XIX, 588.
16	Cancer	Fatty	Absent	Absent	Luithlen, Oser, op. cit.
17	Cancer	Gray, with white portions. Fat with microscope	Absent	Skin bronzed	Mager, Wiener Med. Pr., 1899, XL, 15.
18	Cancer	Fatty	Absent	Absent	Maragliano, Oser, op. cit.
19	Cancer	Very fatty, tenacious, slimy	Present	Present	Marston, Am. J. Med. Sci., 1854, XXVIII, 212.
20	Scirrhus of head, obliteration of duct	Fatty diarrhœa	Present	Present	Martsen, Oser, op. cit.
21	Cancer	Fatty	Absent	Present	Molander and Blix, Oser, op. cit.
22	Enlarged pancreas, marked fatty degeneration	Fatty	Absent	Absent	Notta, Union Méd., 1881, XXXI, 289.
23	Calculus, fibrous pancreas. Duct did not communicate with common duct or duodenum	Gray, greasy, at times solid fat on cooling	Present	Absent	Phillips, Lancet, 1900, II, 104.
24	Cancer	Fatty	Absent	Present	Pott, Oser, op. cit.
25	Fatty degeneration	Oily	Present	Absent	Silver, Tr. Path. Soc., Lond., 1873, XXIV, 121.
26	Cancer	Fatty	Absent	Absent	Roques, Bull. Soc. Anat., 1857, II, 245.
27	Cancer, closed duct	Silvery gray, 25% fat	Absent	Absent	Ziehl, Deutsche Med. Wochnschr., 1833, IX, 538.
28	Rarefied pancreas, obstructed pancreatic duct	Silvery white, consistency of salve	Absent	Absent	Müller, loc. cit.
29	Pancreas appeared like fat. Calculus in duct	Free oil or fat	Absent	Absent	Walker, Med. Chir. Trans., 1889, LXXII, 257.

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Twenty-nine cases of steatorrhoea are the basis of this table. Jaundice was present in twelve and absent in seventeen. Among those with jaundice, tumors, chiefly cancer, were present in eight. The lesions existing in the remaining four cases were a cyst in one, an induration, rarefaction and fatty transformation in three, in which there was also either obstruction or obliteration of the duct. Of the seventeen cases of steatorrhoea without jaundice, in seven the lesions were tumors chiefly cancer; in six calculi were present; two were fatty and two were single examples of cyst and atrophy.

It was considered interesting to note also the relation of diabetes or glycosuria to the steatorrhoea. Diabetes was present in eleven cases and absent in eighteen. The lesions present in the former series were tumors, chiefly cancer, in four, calculi in four, a cyst in two and fatty degeneration in one instance. Among the eighteen cases of steatorrhoea without diabetes were eleven of tumors, chiefly cancer, two of calculi, two of fatty transformation and one each of atrophy and induration. Visible faecal, jaundice and diabetes were present in three cases only, two of tumor and one of cyst. This table, therefore, does not support the view that jaundice is an important factor in the origin of the fatty stools connected with disease of the pancreas. It suggests that in about three-fifths of the cases of steatorrhoea attributable to pancreatic disease, there is neither diabetes nor jaundice, that in two-fifths there is either diabetes or jaundice in about equal proportion and in but few instances is there a combination of diabetes and jaundice.

Müller's researches were of value in another direction by calling attention to the clinical importance of a chemical analysis of faecal fat in cases of suspected disease of the pancreas. A table has been prepared showing the analyses given by him and others of the percentage of fat extracted from the faeces in health, catarrhal jaundice, and in diseases of the pancreas with and without jaundice. The last mentioned include only those actually demonstrated either by the knife or by the passage of a typical calculus.

It is evident from this table that the faeces of the healthy individual contain about 20 per cent. of unabsorbed fat and that in catarrhal jaundice this ratio may be doubled. In affections of the pancreas the percentage of unabsorbed fat is generally not much increased except when jaundice is an accompaniment, thus sustaining the position of Müller. In health this extracted fat contains from 20–30 per cent. of neutral fat and from 70–80 per cent. of split fat, namely, fat acids and soaps. In ten cases of disease of

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II.—Comparative Results of Analyses of Faecal Fat.

Condition.	Percentages of: Extracted Fat.	Fat Acids.	Soaps.	Split Fat.	Neutral Fat.	Authority.
Health, milk diet	21.0	51.3	20.9	72.2	27.88	Müller, Ztschr. f. klin. Med., 1887, XII, 45.
Health, milk diet	....	39.8	40.5	80.3	20.5	
Health, bread and milk	....	25.3	49.7	75.	24.8	
Catarrhal jaundice	43.9	21.6	27.5	48.11	50.83	
Catarrhal jaundice	9.56	....	....	88.59	11.41	Katz, Wiener Med. Wchnschr., 1899, XLIX, 153.
Catarrhal jaundice	21.31	34.54	43.26	77.8	22.1	
Rarefied pancreas, obstructed pancreatic duct. Jaundice	43.9	21.6	27.5	49.1	50.83	Müller, loc. cit.
Necrosis of pancreas	33.3	....	....	29.5	76.1	v. Noorden, Berl. klin. Wchnschr., 1890, XXVII, 1022.
Calculus in pancreas, extensive atrophy. Diabetes	29.04	17.08	5.33	22.41	77.57	Müller, loc. cit.
Calculi, pancreatic, found in stools	....	19.02	38.2	57.4	42.6	Kinnicutt and Herter, Am. J. Med. Sci., 1902, CXXIV, 948.
"Cyst" of pancreas	28.7	30.9	16.8	47.7	52.	Müller, loc. cit.
Cancer of pancreas	33.3	....	....	8.4	91.6	v. Noorden, loc. cit.
Fibrous and fatty pancreas, glycosuria. Jaundice	38.66	....	....	51.42	48.58	Teleky, Wiener klin. Wchnschr., 1902, XV, 741.
Cancer of pancreas, closure of common and pancreatic ducts.	....	73.3	7.1	80.4	19.6	Deucher, Corresp. bl. f. Schw. Aerzte., 1898, XXVIII, 321.
Cancer of pancreas	....	52.1	9.5	61.6	38.4	
Large hard pancreas, small hæmorrhages, necroses. Jaundice	34.22	....	...	13.93	86.07	Katz, loc. cit.
Thick flat mass in pancreas; eventually jaundice	46.76	64.92	17.58	82.5	17.5	Northrup and Herter, Am. J. Med. Sci., 1899, CXVII, 131.

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the pancreas the neutral fat ranged from 17.50–91.6 per cent. In but two of these was the percentage of neutral fat below normal, while in nine of them it was largely or greatly increased. That of split fat, on the contrary, was decidedly diminished in nine out of eleven patients. In the remaining two it was as high as in health. The table, therefore, bears out the view of Müller, though not without exceptions, that in pancreatic disease there is less splitting of the fat and consequently an increase of the neutral fat, thus giving a satisfactory explanation of the oily stools of the older observers.

On the other hand, there is a sufficient lack of anatomical control to permit his conclusions to be accepted without question. Enough pancreatic juice may have been supplied to affect the results of chemical analysis in many of the cases of obstruction of the duct of Wirsung by a flow through the duct of Santorini. If both ducts were closed and the pancreas extensively diseased an accessory pancreas may have existed. Müller himself recognized the influence of intestinal bacteria and gastric contents (Cash, *Arch. f. Anat. u. Phys.*, 1880, 373; Volhard, *Verh. d. Congr. f. Inn. Med.*, 1901, XIX, 302) in splitting fat, although he regarded their importance as slight. It is obvious also, as stated by him, that the faeces may contain an excess of fat, not only in cases of jaundice, but also when there is a superabundance of fat in the food, and when there is disease of the absorbents within or without the intestinal wall.

Steatorrhoea, therefore, is to be regarded as evidence of disease of the pancreas only when other causes of its presence can be excluded, the most important of which is interference with the flow of bile into the intestine. Its recognition depends not merely on the presence of fat resembling oil, butter, lard, or tallow, but in doubtful cases requires the skill and facilities of the chemist trained in physiological methods.

The probability that steatorrhoea due to extensive disease of the pancreas may exist for years without disturbance to the general health, is suggested in the communication of Walker (*Med. Chir. Trans.*, 1889, LXXII, 257). His patient, a physician, free from jaundice, passed for twenty years large colorless stools of a peculiar putrid odor occasionally accompanied by free oil or fat, liquid or solid. During this period he was in perfect health and in the active pursuit of his profession. He died at the age of ninety years. There was no marked emaciation. The pancreas was large, apparently composed of nearly pure fat. The duct was rendered

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almost absolutely impermeable within an inch of the duodenum by a very irregular calculus.

Despite the attention which has been given since the time of Friedreich to azotorrhoea, as manifested by the presence of numerous undigested muscle-fibres in the faeces, but little clinical evidence has been offered that this sign is likely to prove of especial value in the diagnosis of diseases of the pancreas.

In the preparation of the accompanying table, but eight cases have been found which fulfil the demanded requirements. In six sugar was present in the urine, in five there was visible faecal fat, and jaundice was present in two instances. In Lichtheim's case the diabetes patient's diet was composed largely of meat, but diarrhoea existed, a combination sufficiently explanatory of azotorrhoea without the assumption of the presence of disease of the pancreas. The relative frequence of steatorrhoea as compared with azotorrhoea indicates that proteids are better digested than fats if the supply of pancreatic juice is notably diminished. Any significant increase of undigested muscle-fibres in the stools would be expected only when there was extreme diminution of pancreatic juice in the bowel, gastric digestion was relatively normal, the diet contained no excess of meat and there was no diarrhoea.

Bulky stools are mentioned by Oser (*Deutsche Klinik.*, 1901, V, 165) as suggestive of disease of the pancreas. These are notably excessive in quantity as compared with that of the food taken and are composed of unabsorbed muscle-fibres, fat and carbohydrates. He has met with this condition in a number of cases in which the suspicion of pancreatic disease was confirmed.

The various possible disturbances of function in pancreatic disease have usually been sought by inspection and microscopical examination and by the use of the simplest chemical and physical methods. It must be recognized, however, that any considerable disturbance in the digestion and assimilation of fat, muscle and carbohydrates from affections of the pancreas has almost invariably been connected with extensive and protracted lesions. It is obvious, therefore, that feeding with an increased quantity of one or the other of these constituents of diet in suspected cases of pancreatic disease might be followed by appreciable changes in the secretions and excretions earlier than otherwise would have been the case. It is clear, also, that disturbances in the digestion of fats, starches and proteids relieved by the addition of pancreas or its preparations to the diet, provided disease of the digestive glands could be eliminated,

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III.—Relation between Diabetes or Glycosuria, Steatorrhœa, Azotorrhœa and Jaundice in Diseases of the Pancreas.

Condition.	Diabetes or Glycosuria.	Steatorrhœa.	Azotorrhœa.	Jaundice.	Authority.
Cancer secondary to cancer of stomach	Maltosuria	Absent	Present	Absent	v. Ackeen, Berl. klin. Wchnschr, 1889, XXVI, 493.
Only traces of parenchyma. Duct not recognized	Present	Present	Present	Absent	Fles. v. Friedreich, op. cit.
Abscess	Present three weeks before death	Present, resembling cod-liver oil	Present	Absent	Hartley, Tr. Path. Soc., Lond., 1862, XIII, 118.
Calculus	Present	Fat crystals	Present, copious meat diet, diarrhœa	Absent	Lichtheim, Berl. klin. Wchnschr, 1894, XXI, 185.
Cancer	Absent	Present	Present	Present	Oser, op. cit., 87.
"Cyst"	Traces of sugar	Absent	Present	Absent	Riegner, Berl. klin. Wchnschr, 1890, XXVIII, 959.
Indurated atrophied pancreas. Almost complete obliteration of lower part of common bile duct	Present, but almost wholly disappeared after occurrence of jaundice despite carbohydrates in diet	Present	Present	Present	Teleky, Wiener klin. Wchnschr, 1902, XV, 741.
"Cyst"	Absent	Absent	Present	Absent	Müller, loc. cit.

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might furnish additional evidence in favor of the pancreatic source of the disturbance.

It has repeatedly been noted that faecal fat has been observed when the patient was eating abundantly of fat. It is desirable, therefore, in possible cases of pancreatic disease to increase the quantity of fat in the diet nearly to the limit which is to be reached without producing steatorrhoea in healthy persons, or in patients not suffering from disease interfering with the absorption of fat. It is particularly desirable to determine the toleration of fat in those cases of diabetes in which the pancreas presents no abnormal conditions. These limits are not sufficiently known at present, especially as the thorough appreciation of this method of investigation demands the use of especial training and a properly equipped laboratory.

Hartsen (Nothnagel's *Sp. Path. u. Ther.*, 1898, XVII, 21) gave eight to ten teaspoonfuls of cod liver oil to two diabetic patients in each of whom extreme atrophy of the pancreas was found, but there was no unusual quantity of fat observed in the faeces. Müller (loc. cit.), despite an almost exclusive milk diet in his case of cyst of the pancreas, found only a trifling increase in the fat extracted from the faeces and but little variation in the split and neutral fats from that observed when a mixed diet was taken. Herter gave to Northrup's patient with probable cancer of the pancreas an exclusive milk diet. Although the faeces had been regarded as fatty before this test was applied, no chemical analysis of their condition was reported. While the milk diet was being taken (see table) there was a large excess of fat in the faeces, although there was no considerable modification in the percentage of neutral fats. The especial change seems to have been an increase in the percentage of fat acids and a diminution in that of the soaps. The reported cases are few in which pancreatic disease has been found after death and properly controlled dietetic tests with fat have been made during life. Important additions to our knowledge are likely to be made by further observations in this direction.

In like manner should be tested the capacity of the patient for digesting muscle in the intestine as compared with that of the normal individual or with one suffering from affections in which there is no reason for supposing that the pancreas or intestine is diseased. For this purpose it is important first to determine the condition of the gastric functions and then to introduce into the intestine the muscle-fibre as free as possible from the influence of gastric digestion. It may be that the glutoid capsules of Sahli, to be mentioned

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later, will suffice for the latter purpose or that other more satisfactory means may be devised. Müller found well preserved muscle-fibres in his case of cyst of the pancreas when the patient was not eating more meat than a healthy adult could easily digest. A similar appearance was observed during several days while the patient was taking but little meat. The evidence furnished by this patient has only a relative value since the nature of the lesion was determined by a surgical operation and the condition of the pancreatic duct was unknown.

The possibility of testing the efficiency of the pancreas by attempting to produce an alimentary glycosuria also demands consideration. The researches of Wille (*Deutsches Arch. f. klin. Med.*, 1899, LXIII, 546) in this direction are especially significant. This observer gave at breakfast to each of eight hundred patients 100 grammes of glucose in a half litre of tea or coffee. This quantity was selected with the view that the limit of physiological glycosuria lay between doses of 150 and 250 grammes. The urine of the patients was collected every two hours after the glucose was taken. In fifteen of seventy-seven patients who died, glycosuria occurred, and the postmortem examination showed alterations of the pancreas. In certain instances the changes were slight and ascertained only by microscopical examination. The test was positive in three out of four cases of cancer of the pancreas. Unfortunately the ease with which a similar result is obtained with this test in a great variety of conditions in which there is no reason to suspect disease of the pancreas makes it of little value in diagnosis under present conditions (Naunyn, Nothnagel's *Sp. Path. u. Ther.*, 1900, VIII, 1, 21). The comparison of the quantities of glucose necessary and the percentages of sugar obtained may lead to further information.

The functions of the pancreas may be tested also by the use of agents which demand largely the action of the pancreatic juice to promote their absorption and elimination. Salol was first suggested for this purpose by Ewald and Sievers (Ewald, *Klin. d. Verdauungs Krankh.*, 1888, II, 44). It had been stated by Nencki that salol was split by pancreatic juice into salicylic acid and phenol and that the former could readily be detected in the urine. It was recommended that the salol be given in capsule or in pills coated with keratin. A delay in the cleavage would suggest retention in the stomach or deficiency of pancreatic juice. Sahli (*Lehrb. d. klin. Untersuch. Method*, 1899, 440) has suggested the use of "glutoid" capsules containing iodoform to determine the presence of pancreatic secre-

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tion in the intestine. It is claimed that these capsules are sufficiently hardened in formaldehyde to withstand powerful gastric digestion for at least twelve hours, although rapidly digested in pancreatic juice. If there is normal motility of the stomach the iodine reaction will appear in the saliva in from four to six hours after the capsule containing the iodoform is swallowed, provided there is a satisfactory pancreatic digestion and there is no interference with intestinal absorption. He (*Deutsches Arch. f. klin. Med.*, 1898, LXI, 478) reports a number of cases in which the reaction was delayed for twenty-four hours or more and obstruction of the pancreatic duct from cancer of the gland was found.

The late reaction is evidence of defective pancreatic digestion only when there are normal gastric motility and intestinal absorption. If the latter is defective and there is diarrhoea the undigested capsule may be found in the faeces. Fromme (*Münch. Med. Wochenschr.*, 1901, XLVIII, 591) applied this test in a case proving to be one of inoperable sarcoma of the omentum. Visible faecal fat was present, but neither jaundice nor glycosuria. The reaction did not appear till the end of twenty-seven hours. In a second patient, who was found to have a "cyst" of the pancreas, the glutoid capsule test gave only a slightly delayed reaction, from seven and a half to nine hours. Although these cases were reported to illustrate the inaccuracy of the test, the evidence given is insufficient to exclude closure of the pancreatic duct in the first, and it is possible that the "cyst" of the pancreas was an omental bursitis or, if of the pancreas, that there was no considerable interference with the passage of the pancreatic juice into the intestine.

The suggestion is obvious that if symptoms attributable to disturbed functions of the pancreas be present and other conditions, especially jaundice, be absent, the use of pancreatic preparations or of minced pancreas might favorably affect these disturbances and thus indirectly confirm the diagnosis of pancreatic disease. Fles (loc. cit.) gave daily a calf's pancreas to his patient with atrophied pancreas and unrecognizable duct. The fat and muscle-fibres disappeared from the faeces to return again when the pancreas was omitted from the diet. Repeated instances of the disappearance of visible fat from the faeces and of improvement in diabetics have followed the use of pancreas and its preparations, but they are not included in this consideration as lacking the control of anatomical investigation.

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The examination of the urine for pentose has attracted attention since the statement by Hammarsten (*Ztschr. f. phys. Chem.*, 1894, XIX, 20) that the pancreas contained a nucleo-proteid the cleavage of which produced pentose. Salkowski, who had discovered the condition pentosuria, recognized the identity of the pentosazon in the pancreas and that in the urine, and suggested that pentosuria might be regarded as an affection of the pancreas. Blumenthal (*Berl. klin. Wochenschr.*, 1895, XXXII, 567) showed that the condition might be persistent during a period of five months. Pentose was usually sought with phenylhydrazin, acetic acid and heat. Mayo Robson (*op. cit.*, p. 78) states that Cammidge obtained yellow crystals in sheaves and rosettes from the urine of a patient with chronic pancreatitis, by boiling it for a short time with an oxidizing agent and adding phenylhydrazin. Urine from a case of catarrhal jaundice gave a negative result when similarly treated. It was suggested by him that this test might prove useful in diagnosis. Further evidence is needed before any diagnostic importance in connection with pancreatic disease is to be attached to the presence of these crystals, since anosazon of similar appearance has been obtained by the action of phenylhydrazin on normal urine. Blumenthal, moreover (*Berl. klin. Wchnschr.*, 1897, XXXIV, 245), was able to isolate nucleo-proteids from various organs and find pentose in them, which obviously excludes the pancreas as the necessary place of their origin.

It is known that the putrefaction of the proteid contents of the intestine is caused by bacteria and that their action is enhanced by the presence of pancreatic juice. In consequence the aromatic compounds indol, skatol and phenol are formed, and the quantities of indican and of ethereal sulphates in the urine give evidence of the extent of the proteid putrefaction and indirectly of the condition of the pancreas. Gerhardi (*Virch. Arch.*, 1886, CVI, 303) observed an absence of indican in the urine in a case of obstruction of the small intestine, in which condition, according to Jaffé, it should have been increased. After the patient's death acute hæmorrhagic pancreatitis and an obstructed pancreatic duct were found. Gerhardi suggested that the absence of indican when the small intestine was obstructed might be regarded as evidence of disease of the pancreas. Two confirmatory and one contradictory observations have been made. Oser, however, maintains that variations in the excretion of indican may have no direct relation to disease of the pancreas, hence be of no diagnostic value.

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The quantity of ethereal sulphates eliminated seem to have a more constant relation to the extent of intestinal putrefaction and to the secretion of pancreatic juice. The clinical observations on these points, especially those sufficiently controlled, are few. Herter found increased indican and an increased ratio of ethereal to pre-formed sulphates in Northrup's case, in which disease of the pancreas, though not the condition of the duct, was ascertained. Edsall (*Am. J. Med. Sci.*, 1901, CXXI, 401) concludes in his communication on this subject "if, with suspicion of pancreatic disease, factors which usually cause an increase of the ethereal sulphates be present and yet the values be found low, the test would at present appear to be of distinct practical importance in diagnosis. Constipation, gastric hypoacidity or anacidity, icterus, grave anaemia, and cachexia are very likely to cause an increase in the relative or absolute values of the ethereal sulphates."

Finally, Opie (*J. H. H. Bull.*, 1902, XIII, 117) has suggested the possibility of discovering in the urine the fat-splitting ferment set free in acute pancreatitis. He endeavored to determine its presence in one case by following the method proposed by Cassell and Loevenhardt, which is based upon the decomposition of ethyl butyrate by the ferment and the production of butyric acid. The urine neutralized with potassium hydroxide was divided into two portions, one of which was boiled for the purpose of destroying the ferment. Ethyl butyrate was added to each specimen. That unboiled after twenty-four hours gave an acid reaction, while the boiled specimen showed little, if any change.

The symptoms which have proven most useful in diagnosis are those which call attention directly to the region of the pancreas. They are the epigastric pain, tenderness, tension and tumor, with or without obstructive jaundice, and evidence of mechanical interference with the motility of the stomach and duodenum.

Pain, when present, usually is manifested early in the course of the disease and may be the initial symptom. It often suggests gastric cramp or intestinal or biliary colic. It is occasional, paroxysmal or persistent, dull or sharp, squeezing, tearing or piercing, mild or severe, even agonizing and not infrequently is associated with signs of collapse. It may be clearly defined near the median line, midway between the ensiform cartilage and the navel, or may shoot laterally, especially towards the left side. It occasionally is continued upwards into the thorax or downwards into the lower abdomen.

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Tenderness is a frequent accompaniment, especially of persistent pain. It often is described as sensitiveness and although usually limited to the epigastrium may be found in the region of the spleen or in the left groin. Ultimately tender spots may appear in remoter parts of the abdomen, especially when disseminated foci of fat necrosis accompany the pancreatic affection.

Epigastric tension often is observed and may be apparent at the outset or develop later in the course of the disease. When an early symptom it is followed soon by a circumscribed, tympanitic, epigastric swelling, evidently due to gaseous distension of the stomach. The resistance found late in the course of pancreatic disease is due to the formation of a tumor. When the latter is the result of disease of the pancreas its characteristics depend largely upon the nature of the affection. Small, circumscribed, dense tumors result from chronic inflammation or neoplasms, usually of the head of the gland, while large, tense tumors of pancreatic origin in the left half of the epigastrium or symmetrically involving more or less of the upper abdomen are indicative generally of cysts of the pancreas or of collections of fluid in the omental bursa, more common than the former and generally confounded with them.

Jaundice, commonly slight and of short duration, is occasionally encountered in acute affections of the pancreas. Then it is oftener seen in the course of a few days after the onset of the attack than as an earlier symptom. Prolonged jaundice is a frequent accompaniment of chronic affections of the head of the pancreas, especially of fibrous inflammation and neoplasms. The association of the jaundice with distension of the gall bladder is sufficiently frequent, as noted by Courvoisier and others, to make this combination suggestive rather of disease of the pancreas than of affections of the biliary tract.

Motor disturbances of the stomach and intestine are among the usual symptoms associated with pancreatic disease. Vomiting, sometimes frequent or incessant and often distressing, is customary among the early symptoms of acute pancreatitis, and constipation, at times obstinate, is the rule. So constant are these motor disturbances that the frequent diagnosis in cases of acute pancreatitis is acute intestinal obstruction.

The prolonged motor insufficiency of the stomach mechanically induced by chronic affections of the pancreas, especially from enlargement of the head of the gland, not infrequently gives rise to dilatation of the stomach. In consequence frequent or persistent vomiting may take place late in the course of pancreatic disease.

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Although the diagnosis of diseases of the pancreas, in the light of our present knowledge, practically depends more on the symptoms calling attention to the locality of the organ than upon the evidence of disturbances of its function, it is reached eventually by the exclusion of other sources of the local symptoms than the pancreas.

The differential diagnosis lies first between acute and chronic affections and second between the several varieties of chronic pancreatic disease. The former include pancreatic hemorrhage and the hemorrhagic gangrenous and suppurative varieties of acute pancreatitis, all of which are characterized by similar symptoms and some of which presumably represent stages of the same affection. The latter include chronic pancreatitis with or without calculi, cysts and tumors.

Of acute pancreatitis it may be said now as in 1889 (Fitz, Acute Pancreatitis. The Middleton-Goldsmith Lecture for 1889), "The symptoms are essentially those of a peritonitis beginning in the epigastrium and occurring suddenly, during ordinary health, without obvious cause. The diagnosis, therefore, is based on pain, tenderness and tympany limited to the region of the pancreas, and on the gradual development of a deep-seated peritonitis in the same place.

Differential Diagnosis.

The differential diagnosis lies, practically, between an irritant poison, perforation of the digestive or biliary tracts, and acute intestinal obstruction. An irritant poison is excluded by the history of the case, and by the examination of the vomit. Perforating ulcer of the stomach or duodenum is to be excluded by the absence of pain after eating, hæmorrhages from the digestive canal and cachexia. Acute perforation of the transverse colon is rare, and the resulting peritonitis progresses more rapidly and is likely to be general. Perforation from gallstones is usually preceded by attacks of biliary colic and jaundice, while the seat of the pain is rather in the region of the gall bladder than in that of the pancreas. Acute intestinal obstruction is most likely to give rise to doubt. It is to be eliminated by determining the patency and capacity of the large intestine, by the rarity in the epigastrium of an obstructed small intestine, by the immediate presence of localized tenderness, and by the usual absence of conspicuous, general tympany or limited distension of intestinal coils."

In the cases of acute pancreatitis thus far reported, no new evidence, unless that of Opie be confirmed, has been furnished which gives to the diagnosis more than a variable degree of probability.

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Certainty has been reached only by a laparotomy or a postmortem examination. The former has made clear the condition of the pancreas by the usual disclosure of multiple areas of disseminated fat necrosis, a condition occurring on an extensive scale only in the sequence of acute pancreatitis, or by the demonstration of the enlarged, hemorrhagic or necrotic pancreas as the focus of the surrounding peritonitic manifestations. Fortunately the exploratory laparotomy in an increasing number of cases has proven the most satsifactory method of treatment and, like most abdominal operations for the relief of acute symptoms, is the more helpful the earlier in the course of the disease it is performed.

The diagnosis of chronic pancreatic affections is based usually on the occurrence of localized pain and upon the presence of a tumor. The pain may exist without the tumor, but the latter is rarely present without the former at some time during its formation. The pain of chronic pancreatic affections is often a deep-seated discomfort; when severe it is likely to be paroxysmal and then is suggestive of biliary colic, but is referred rather to the region of the pancreas than to that of the biliary tract. The tumor is of slow or rapid growth, large or small, perhaps distinctly palpable only in narcosis, fixed or slightly movable, with or without symptoms of pressure upon the surrounding parts. Its position behind the stomach and above or behind the colon is made apparent by inflation and percussion of these portions of the alimentary canal. Evidences of disturbance of pancreatic function are to be sought along the lines previously mentioned, but experience has shown that definite and convenient additions to our knowledge must be made before functional disturbances of the pancreas can be ascertained sufficiently early and with sufficient certainty to render assured the pancreatic source of the disease. The discovery of sugar in the urine should lead to the examination of the faeces for fat. The presence of the latter should suggest the search for undigested muscle-fibres and for glycosuria, and alimentary and therapeutic tests should be applied to all suspected cases.

The differential diagnosis lies between chronic pancreatitis with or without pancreatic calculi, cysts and tumors.

The association of jaundice with tumor has led to the diagnosis of chronic pancreatitis and to its effective treatment by Mayo Robson and others. The relatively rapid formation of the tumor in the sequence of symptoms suggestive of gallstones may serve in certain instances to differentiate this condition from malignant neoplasms. The discovery of characteristic calculi in the faeces has made clear

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in a few instances the source of discomforting or severe symptoms without tumor in the region of the pancreas, and exploratory laparotomies have confirmed or suggested the diagnosis of neoplasms of this organ.

The various possibilities of a more accurate study of the symptomatology and diagnosis of diseases of the pancreas suggest an early advance in our knowledge of the subject. With the increase of clinical laboratories in our general hospitals, and with the more frequent addition of biological chemists to the force of pathologists, the errors of the past are likely to be avoided and new lines of research are sure to be planned.

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THE PANCREAS AND PANCREATIC DISEASES.

SURGERY OF THE PANCREAS: WITH ESPECIAL CONSIDERATION OF TRAUMA AND INFLAMMATORY PROCESSES.

BY JOH. VON MIKULICZ-RADECKI, M.D.

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When the President invited me six months ago to present a paper on the surgery of the pancreas before to-day's assembly, I hesitated as to whether I would be able to do justice to the honor he showed me. There were two reasons for doubting whether I could fulfil the expectations. Above all, it would not be easy for me to speak on the surgery of the pancreas in a country where so many of its most prominent pathologists, physicians and surgeons have in recent years devoted themselves to careful investigations along this line. One can justly say that the advancement of our knowledge on this subject during the last few years is mainly due to the efforts of American pathologists and surgeons. I need only mention the names of Fitz, Flexner, Halsted, Hardin, Lund, Opie, Osler, Park, Senn, Thayer, Tilton and H. U. Williams, of whom fortunately a number take an active part in to-day's proceedings.

A second reason for embarrassment in taking up this subject is the fact, that operative interference for disease of the pancreas is still at the present time the most incomplete chapter in the realm of abdominal surgery. It is scarcely twenty years since Gussenbauer described the first operation for cysts of the pancreas. For many years the surgery of this organ was confined to the treatment of this affection, which was a comparatively easy task so far as the technique was concerned. In regard to the other pancreatic affections, as trauma, inflammatory conditions and new growths in the narrowest sense of the word, it is only in the last ten years that surgical treatment has been seriously undertaken. So recently as 1891 and 1892, the anatomists von Gerlach and Joessel dismissed the subject of the topographical anatomy of the pancreas in a few words, stating that the organ had no clinical interest, as it was almost impossible for the surgeon to reach it.

Still another difficulty presents itself to the surgeon who reports on affections of this organ. When we make an exception of the cystic condition, it is very seldom that one, with our present knowl-

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edge, has an opportunity to operate upon the diseased pancreas. Hence, the personal experience of each surgeon is only small, and a comprehensive report must rest in a great measure upon the observations of others. When I look over the notes of my own cases of pancreatic surgery during the last twelve years, I find that there are about sixty. This considerable total for a single surgeon is, however, materially reduced when I exclude thirty cases in which malignant disease of the stomach, for which I did resections, had involved the pancreas. However, the observations made in these cases are not without importance to our subject, and I shall refer to them later.

When we seek the cause of the tardy development of the surgery of the pancreas, we find we can ascribe it principally to three general reasons which we must consider carefully, as they show us that which we may expect from this branch of surgery in the future.

First, the topographical relations of the organ should be considered. The hidden and protected position of the pancreas accounts for the infrequency with which it is injured. When such, however, is the case, there usually exist severe complicating injuries of neighboring organs and the patient very often dies either from shock or from hemorrhage before the surgeon has the opportunity to interfere. But when the abdomen is opened in such cases, the accompanying injuries of the surrounding parts almost always demand such attention that the lesion of the pancreas is easily overlooked. Its protected position makes the technique of bringing it, or portions of it, to the surface of the body exceedingly difficult when no changes from disease are present which approximate the organ to the abdominal walls, for example, in pancreatic cysts. We possess, therefore, no such typical operative methods like those which we employ in exposing the kidney, gall-bladder or vermiform appendix, whereby the pancreas can be made accessible, and which would be looked upon as normal methods. According to the location of the diseased part and to the enlargement of the organ in a certain direction, we are compelled to reach the pancreas by various routes, and in this we are, moreover, hindered by the interposition of many organs that surround it.

The operative methods by which we can expose the pancreas may be divided into two general groups: first, the trans-peritoneal, and second, the retro-peritoneal.

In the trans-peritoneal methods, one enters through a median or lateral incision in the anterior abdominal wall, and then either

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through the gastro-colic ligament, the ligamentum gastro-hepaticum, or, after pushing up the omentum and transverse colon, through the meso-colon. In each case the omental bursa is opened. A fourth trans-peritoneal method (employed by Koerte) is to force one's way along the side of the duodenum, the peritoneal covering of which must first be incised. By this last method, of course, only the head of the pancreas can be conveniently exposed. The retro-peritoneal methods aim to reach the pancreas by incisions in the lumbar region. By this means one is enabled to expose only the head or tail of the organ, and the method should therefore be employed only when through changes by disease the affected part is pushed farther to one side or is enlarged as in abscesses, cysts or tumors.

Another difficulty which we have to contend with is the results from the location of the pancreas, owing to the possibility of severely injuring surrounding organs when we attempt to reach the pancreas. Besides the stomach and transverse colon, which lie in front of the pancreas, the common bile duct, the duodenum, and the large blood vessels demand attention; not less the middle colic artery, the injury of which is followed by gangrene of the transverse colon, a fact which Kroenlein has first demonstrated by his anatomical studies.

Another fact which has prevented the advancement of pancreatic surgery is the difficulty in diagnosis. Here, also, the concealed position of the organ is the main obstacle. The result of examination by palpation is often absolutely negative, in most cases indefinite, and even when the organ is much enlarged and readily felt by the hand as the result of disease, the interpretation is usually uncertain.

The subjective symptoms are just as indefinite. I must not permit myself to discuss further the difficulties of diagnosis, as the preceding speakers have already discussed it more fully. I only wish to advance the statement that the surgeon cannot rely on the disturbance of function, in most cases, as a diagnostic sign of value. According to our experience, signs of functional disturbance in this enormously important organ do not appear until the greater portion of the gland is affected. Then the surgeon has no longer any right to interfere, for, when once a pancreatic diabetes or symptoms of severe disturbance of its fat-digesting function develop, the patient is, as a rule, beyond the help of operative measures. Experience, in fact, has shown that in affections of the pancreas, which have been treated surgically, positive functional disturbances have been observed only in rare instances. The surgeon can not, unfortunately, watch the further course of the disease as the medical clinician does,

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but he must on the contrary decide upon the operation, particularly if it be a question of surgical interference, while the general condition of the patient is still satisfactory. So at the present time most cases are operated upon when the diagnosis is only probable, and only after the abdominal cavity has been opened can a differential diagnosis be made. As is well known, in the beginning of the era of pancreatic surgery, most operations were undertaken on a false diagnosis; to-day as soon as an affection of the pancreas is deemed probable, it is considered wise to submit the patient to an exploratory laparotomy. This practice fortunately is of no great consequence because, as a rule, when the pancreas is intact, we find other injuries or diseases present which justify laparotomy.

A third reason which has prevented the rapid development of pancreatic surgery is that the operation, so far as it includes the organ itself, is much more dangerous that an operation upon any other abdominal organ. This is partly the result of the fact that in most diseases of the pancreas, with the exception of cysts, the general condition of the patient is so low that his recuperative powers are markedly diminished.

A further danger lies in the peculiar physiological character of the gland itself. Two points come into consideration here. The pancreas is very rich in blood vessels, and hemorrhage from an injury is difficult to control. Simple tying of the fragile tissues is insufficient, and one must stop the bleeding with sutures deeply buried in the tissues and including much of the latter, which has the disadvantage of causing the parenchyma to necrose, thereby creating conditions which will be shortly discussed.

In spite of deep sutures and heavy ligatures *en masse*, blood and pancreatic secretions ooze into the peritoneal cavity, preventing the formation of peritoneal adhesions, which in abdominal operations in general are so important a protection. Secondary hemorrhage into the peritoneal cavity is very apt to occur. Several operations are recorded in medical literature which seemed to promise a favorable result, but which ended fatally from this complication.

A danger much greater than that from hemorrhage complicating operations on the pancreas, is that due to the special secretion of the gland leaking from the injured parenchyma in larger or smaller quantities. The point as to whether or not this leakage is injurious, was only recently definitely settled. After the experiments and experiences of recent years, we can no longer doubt that such leakage is indeed harmful. The experimental studies of Williams, Flexner,

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Biondi, Katz and Winkler and others, show clearly that injuries of the pancreas, through which the vitality of a part of the organ is impaired, and the flow of pancreatic juice toward the pancreatic duct is hindered or ceases entirely, seriously affect the peritoneum and the neighboring tissues. Fat necrosis, as well as the various forms of pancreatic inflammation, from a severe hemorrhagic pancreatitis to a chronic induration, may be experimentally produced in animals by such injuries. As this point has been thoroughly discussed by the previous speakers, I will not consider it further. I must, however, direct your attention to the fact that a number of reliable clinical observations are on record, in which, after accidental injuries, changes were present in the pancreas and the neighboring organs similar to those which we have just considered in connection with the experimental work on this subject. When death does not ensue from hemorrhage, in such cases, a fatal result may occur from the acute, subacute or chronic forms of pancreatitis following such injuries. I can mention in this direction the observations of Simmonds, Schmidt, Hahn, Gessner, Pressel, Sendler, Groeningen, Leith, Ziegler and Selberg. Even after injury to the organ during operation, fat necrosis has been observed, as in Koester's case. That enormous quantities of pancreatic secretion can escape from the wound surfaces of the pancreas, is proved by the interesting cases of Ruggi and Biondi, who resected a large portion of the pancreas for a malignant tumor and drained the wound.

How much worse the prognosis of an operation becomes when the pancreas has been injured, is shown by my statistics of gastric resections in cases of cancer. In ninety-one cases of resection of the stomach where the pancreas was certainly not injured, twenty-five, or 27.5 per cent., died as the result of the operation. In thirty other cases the pancreas was injured. This was usually due merely to freeing the tumor from adhesions to the pancreas. The parenchyma of the pancreas, however, was exposed and communicated freely with the abdominal cavity. In other cases pancreatic lymph glands or superficial parts of the pancreas were removed. Of these thirty cases, twenty-one, or 70 per cent. died, mostly of peritonitis.[1]

If we ask ourselves whether the secretion from the injured pancreas leaking into the abdominal cavity can of itself so damage

[1] It might be said that the mortality of these thirty cases was high on account of the severity and length of the operation. This objection would be just, if the majority of cases had died in collapse, which was not the case. As already stated, the majority died of peritonitis.

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the peritoneum that death from this cause alone may result, we must surely admit that this is a possibility, as shown by a number of experiments and clinical observations of accidental injuries in man. The pancreatic juice mixed with blood has, no doubt, a very toxic effect and can, in the so-called apoplexy of the pancreas, result fatally without the complication of bacterial infection.

In the majority of cases, the secretion from the pancreas—I do not refer to the normal physiological secretion but rather to the exudate from the injured organ—does not flood the abdominal cavity in such quantities that it will prove fatal by mere absorption. It acts indirectly by reason of the local irritation of the peritoneum in that it prepares a nutrient medium for bacterial invasion and makes infection extremely easy.[1]

Even with the present status of our aseptic technique it is not possible to prevent all germs from reaching the abdominal cavity during laparotomy. An uninjured peritoneum will resist this infection if the germs are not introduced in certain quantities. But if the vitality of the peritoneum has been impaired by the action of the pancreatic secretions, then a very limited number of bacteria are sufficient to cause peritonitis.

There is also in every case of injury of the pancreas, the danger of a retrograde infection from the duodenum through the ductus pancreaticus. It seems, moreover, that the secretion from the injured, or also inflamed pancreas without bacterial invasion, can cause a variety of aseptic peritonitis. This is frequently followed by a paralysis of the intestines, leading to rapidly developing intestinal obstruction which often so modifies the symptoms as to lead to a serious mistake in diagnosis.

[1] Not only the normal constituents of the pancreatic juice, chiefly pancreatin and steapsin, come into consideration, but also the direct degeneration products of the dead gland cells. The latter should not be confounded with the pancreatic secretion, as has apparently been done by a number of experimenters; for example, Senn decided, from his experiments in which he made an internal pancreatic fistula, that injuries of the pancreas are without special influence upon the abdominal cavity. It is not correct to assume that the juice of any crushed or powdered gland is identical with its normal secretion. A large number of investigators have observed that when the excretory duct of the pancreas be ligated, and retention of the glandular secretions results, the typical signs of fat necrosis of the pancreas do not appear. This is explained by the fact that the normal or nearly normal secretion is carried away in the lymph and blood stream, where its ferments are rendered harmless, as the investigations of v. Nencki and Tschepurkowski have shown.

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I speak of this point more in detail because I consider it of great importance in pancreatic surgery. For whatever operation may be done on the pancreas, we must take the greatest pains to keep the secretion of the injured gland from getting into the abdominal cavity. This can be done in two ways: first, one can turn the injured part inwards and close it with deep sutures so that the peritoneal covering is again in continuity. Ninni used this method with good results in a gunshot wound. As a rule, however, this will not be possible or, at least, will not offer a sufficient protection against leakage of the pancreatic juice into the peritoneal cavity. Nothing more can be done in these cases than to protect the latter by means of tampons reaching down to the exposed pancreas.

The value of this tampon drainage is demonstrated to-day by the limited number of wounds of the pancreas which have been operated upon. Of 12 injuries, partly the result of blunt force, of stab or gunshot wounds, 8 were drained.[1] Of these 6 recovered and 2 died. Of the 4 undrained cases, 3 died, only the previously quoted case of Ninni recovering.

When capillary drainage of wounds of the otherwise healthy pancreas is so important, there can be no doubt of its greater value in operations upon the diseased organ. This obtains not only in acute and chronic inflammatory conditions due to bacterial infection, but also in certain aseptic lesions which present themselves to us clinically as pancreatic apoplexy in the most acute cases, or in the more chronic as pancreatic cysts. The admixture of blood to the pancreatic secretion in the peritoneal cavity renders the condition more serious. We see, therefore, that when patients survive the acute stage of the disease, whether septic or aseptic, this is accomplished only through the walling off of the focus of disease by peritoneal adhesions.[2]

[1] These are the cases of

Hahn: Deutsche Ztschr. f. Chir., Bd. 58, 1901.
Kuttner: Beitr. z. klin. chir., Bd. 32.
Villiere: Bull. de la soc. anat. de Paris, Bd. 70, 1895.
Rose: Deutsch. Ztschr. f. Chir., Bd. 34, 3. 36.
Hadra. New York Medical Record, 1896.
v. Mikulicz: Viertalj.-Schr. f. ger. Med. (3), XVIII, 2.
Michaux: XIII intern. med. Kongr. zu Paris.
Cushing: Ann. of Surgery, p. 69 (1898), S. 337.

[2] Recently Pierre Achalme has made experimental studies on the action of pancreatin in the peritoneal cavity. He tried to discover whether the blood serum of the animal experimented upon did not possess some anti-fermentative virtue, and if it could produce immunity when given in increasing doses. He

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I have attempted to collect all operations for acute disease of the pancreas to determine, if possible, the value of drainage also in such cases. I have succeeded in finding 30 cases. In 27 of these, it is distinctly stated that the exposed pancreas was drained; of these, 11, or 38 per cent., died. In the remaining number, either no drainage was established, or exact statements are lacking. Of these, 41, or 80 per cent., died.[1]

From these statistics, we should conclude that wherever the pancreatic tissue has been exposed at all, the abdominal cavity must be tamponed, and drainage established.

After these general remarks, we will proceed to the special part of our subject. We can divide pancreatic diseases which concern the surgeon into three great groups, (1) Injuries; (2) inflammatory processes; and (3) new growths.

In the second group I would include also, pancreatic apoplexy and pancreatic calculi; in the third group we will place in addition to tumors, as is generally customary, the pancreatic cysts which, although in a great number of cases of traumatic origin, in others are certainly due to small apoplexies or to an inflammatory condition.

I have arranged with my colleague, Dr. Roswell Park, who has a paper on the same subject, to confine my remarks to injuries and inflammatory processes, while he is to consider the important class of pancreatic neoplasms, including pancreatic cysts.

As I have repeatedly spoken of the injuries of the pancreas, I can now be more brief, particularly as the number of cases on record is even, at the present time, very small. The problem presented to the surgeon by an injury of the pancreas to-day is very clear. We have first to stop the hemorrhage, and secondly, to prevent, as much as possible, the flow of pancreatic secretion into the abdominal cavity and the subperitoneal tissues. The first and, to some extent, the second problem, will be solved by deep sutures and ligatures *en masse*. Where a break in the continuity of the organ through a stab- or gunshot-wound occurs, we close the wound with deep sutures and thereby best control the bleeding and leakage of pancreatic secretion. When the pancreas, as usually happens by the

was not only successful in rendering animals thus treated immune against toxic doses of pancreatin, but also in obtaining a serum that immunized other animals. Perhaps a serum acting similarly on human beings might be obtained. This would enable us to protect the patient to be operated upon, against the harmful effect resulting from absorption of his own pancreatic secretions.

[1] In the last category, it is possible that a number of drained cases are included, and therefore, the resulting mortality turns out too favorable.

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action of blunt force, is not simply torn but crushed, these means will not be sufficient.

Here as in all unsutured wounds of the pancreas, we must of necessity use the tampon to overcome the dangers previously discussed. Even when the wound is sewed, tamponing is to be recommended, especially when neighboring portions of the stomach or intestines are injured, this being a frequent complication. In spite of prompt suturing of wounds of the stomach and intestine, the danger of peritonitis is very great.

The diagnosis of these cases can rarely be made with any degree of certainty. The difficulties which we contend with in this respect are so great owing to the fact that in most cases the neighboring organs are also injured. In cases which come under observation very soon after injury, we can only suspect a lesion of the pancreas. The surgeon must, however, always bear in mind the possibility of injury to the pancreas in all cases where the force has acted upon the epigastric and umbilical region. He must always direct his attention to the pancreas if, after opening the abdomen, he finds a lesion of another organ, such as the stomach. We often find cases reported where, wounds of the stomach or intestines having been sutured, death has occurred from an undetected wound of the pancreas.

With the uncertainty of diagnosis it is best to make the incision, as a rule, in the median line above the umbilicus. This is also true for penetrating wounds which lie some distance from the median line. From this median incision one can best determine what changes are present in the peritoneal cavity and can enlarge the incision above, below, or to one side, as needed, exposing the injured pancreas according to the location of the injury. Then we can proceed as in wounds of other abdominal organs. I want, in this connection, to mention the great importance of thoroughly washing out the peritoneal cavity with warm normal salt solution (0.9 per cent.).

I have found in all 45 cases of pancreatic injury, 21 penetrating wounds, and 24 subcutaneous wounds from blunt force. Of the 21 penetrating wounds, 12 were of gunshot origin and 9 were stab-wounds. Of the gunshot wounds, 5 were operated upon, 2 dying and 3 recovering. (The cases of Otis, Hahn and Ninni.) The 7 that were not operated upon died. The 9 stab-wounds were all operated upon, 1 dying and 8 recovering. This remarkably favorable percentage of recovery in the stab-wounds is to be explained

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by the fact that, in seven cases, the pancreatic injury was really a prolapse, and in some of these cases only a very minor lesion of the prolapsed portion was present. The evil consequences of injuries to the pancreas within the peritoneal cavity could therefore not follow. The operation in seven cases of pancreatic prolapse consisted in excision of the dislocated portion in five cases and reposition in the other two cases. An intra-abdominal punctured wound of the pancreas occurred only in the cases of Hildebrand and Küttner. In the latter recently published case, the organ was almost completely divided in an antero-posterior direction. Küttner united the divided pancreas by means of two deep and one superficial suture; the hemorrhage stopped at once; then, a wound in the stomach, nine centimeters long, was sewed up and finally the omental bursa was drained with a tampon. The case recovered, even though it was complicated by the formation of a subphrenic abscess.

In Hildebrand's case there was also a perforation of the stomach in addition to the injury to the pancreas. The wound in the stomach was sutured and the bleeding vessels of the pancreas were ligated. No drainage was established, and the patient died four days after laparotomy.

Of the 24 subcutaneous injuries, 13 were not operated upon and all died. Of the 11 operated on, 7 recovered. Three cases were operated upon early, within four days after the injury. One of these recovered (Hadra) and 2 died (Villiere, Michaux).

The operation consisted in exposing the injured pancreas and in drainage; eight times the operation was done late. After one or more weeks the hematoma arising from the pancreatic wound was opened and partly drained. Two cases died (those of Braun and Czerny) and six recovered (the cases of Rose, Mikulicz, Stern, Lissjanski, Michailow, Cushing and Kuhlenkampf).

These figures include only the severe contusions of the pancreas in which the diagnosis was confirmed by autopsy or by an operation undertaken sooner or later. There is, therefore, no doubt that not infrequently slight contusions of the pancreas result from injury which either heal spontaneously or cause only minor disturbances. We must assume this possibility from experiments on animals. The cases in which traumata play an important rôle in the etiology of the different forms of acute and chronic diseases of the pancreas also teach us this lesson. This is especially the case in pancreatic cysts, of which about one-fourth are of traumatic origin, or, at least, referable to traumatic hematomata. But I will not encroach

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upon this subject further, as my colleague will probably thoroughly discuss it. What concerns us here is, that not every injury of the pancreas justifies a bad prognosis, nor does it warrant us in assuming that immediate recourse should be had to operative interference. The indication for operation does not only depend upon the diagnosis of an injury to the pancreas itself, but also upon the severity of all the symptoms, especially and particularly, the steady accentuation of such symptoms. These symptoms are increasing anaemia, the physical signs of blood in the abdominal cavity and peritoneal irritation. An injury to neighboring organs can frequently occasion the same symptoms, as I have previously stated, and, as a rule, it is not important to diagnose that the pancreas itself is injured. The diagnosis of an abdominal injury which can result in the death of a patient from hemorrhage and peritonitis is in general sufficient. No definite rules can therefore be laid down as to whether one should await further developments or proceed immediately to laparotomy in any given case. The suspicion of a severe injury to the pancreas should encourage us to act quickly.

The figures previously mentioned, small as they are, teach us that severe injuries to the pancreas, which are not submitted to operation, terminate fatally almost without exception. They also teach us, in view of the favorable results obtained up to the present time, to make an exploratory laparotomy whenever there is a question of severe pancreatic injury.

We will now proceed to the inflammatory lesions of the pancreas.

It is not my privilege to discuss their etiology and pathology, as the previous speakers have undertaken this task.

I must, however, briefly express my ideas on the subject, particularly as this is a field in which the surgeon has had but little practical experience. He cannot proceed towards a definite end without having a clear idea of the pathological processes which he must combat with the knife.

A very excellent pathological classification of acute pancreatitis by Fitz has stimulated further research on the subject. That author divided pancreatitis into the hemorrhagic, the suppurative and the gangrenous varieties. This division is, however, not the best for the clinician. These three forms of pancreatitis, easily differentiated as they are in typical cases, merge into one another in most instances, or follow each other in succession. Even pancreatic apoplexy is very difficult to differentiate from hemorrhagic pancreatitis.

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Furthermore, the acute and subacute forms of pancreatitis frequently border on chronic pancreatitis. I should, therefore, rather accept the classification of Robson from the clinical standpoint of acute, subacute and chronic pancreatitis. The classification of Fitz into hemorrhagic, suppurative and gangrenous pancreatitis rather represents different stages of the disease, with a common etiology.

Let us now turn to acute pancreatitis, and first of all inquire if it is purely an infectious process, and whether it is exclusively the result of an invasion of bacteria. Without doubt, bacterial infection in acute pancreatitis plays an important rôle, but it does not alone explain the singularly severe symptoms. In this connection, the cases of genuine pancreatic apoplexy, which run their course as an acute hemorrhagic pancreatitis, are of great importance. As is well known, a severe hemorrhage from the pancreatic and retroperitoneal cellular tissue occurs in these cases, as the result of a peculiar dyscrasia of the patient, accompanied by hemorrhagic peritoneal exudation, which is not of bacterial origin.[1] That a hemorrhagic diathesis, or that other predisposing factors, as alcoholism, arteriosclerosis, syphilis, or fatty degeneration of the organ in obesity, play a great rôle, is not to be doubted, but does not explain the nature of the process. If we look for an analogous condition we find it, as the term "apoplexy" expresses, only in the spontaneous hemorrhages in the brain, but here the severe local reactions are missing.

There can be no doubt that there is in addition to the hemorrhage some special cause for this phenomenon. We may not be amiss in attributing it to the action of the pancreatic and fat-splitting ferments upon the gland, which is the seat of an hemorrhage or has been otherwise injured.

As a result of a slight blow the following vicious circle may develop not only in those unusually rapidly fatal apoplexies, but also in small and harmless hemorrhagic foci (of traumatic and non-traumatic origin): small hemorrhages or disturbances in circulation

[1] Hlava found that in so-called pancreatitis acuta, the hemorrhagic exudate in the pancreas, as well as the peritoneum, was sterile. In medical literature the terms "pancreatic apoplexy" and "acute hemorrhagic pancreatis" are frequently confounded, which can be explained by the great similarity of the clinical course as well as the anatomical findings in both affections. My opinion is that a sharp differentiation can only be based upon a bacteriological examination. The one is an aseptic, the other a septic process. The possibility of transitional forms lies in the fact that an infectious pancreatitis assumes a severe hemorrhagic character as the result of a dyscrasia similar to that which we see in a pure pancreatic apoplexy.

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(from arterio-sclerosis, embolus, thrombosis); from this necrosis of a small area of the gland; infiltration around this focus of the ferments set free by the destruction of the parenchyma cells; digestive changes in the surrounding tissue and its vessels which were, until this time, unchanged; enlargement of the hemorrhagic focus, partly as a direct result of the erosion of the vessels, and partly as the result of the undermining of the tissues and the increased pressure from the hematoma; necrosis and destruction of the surrounding parenchyma of the gland; further escape of the ferments, etc., etc. The tendency to successive enlargement of all existing hemorrhagic foci is present beyond doubt. It has already been mentioned, in speaking of the difficulty with which traumatic hemorrhage from even small vessels of this organ is controlled.

Whether a primary focus involves only a small area and heals naturally; whether it slowly enlarges and later, after weeks and months, forms a pancreatic cyst, or finally gives rise to pancreatic apoplexy, depends on the resistance of the vessels and the interstitial connective tissue (fatty degeneration of this tissue is known to be a predisposing factor); upon the digestive activity of the escaping ferment, and finally, upon the anti-fermentative property of the blood serum and the other body fluids.

I should like to emphasize the fact that in true pancreatic apoplexy, owing to the existing serious constitutional dyscrasia, a surgical procedure would hardly be warranted. As it is difficult, clinically, to distinguish these cases from cases of acute pancreatitis, it will occasionally happen to the surgeon to operate upon the former under a mistaken diagnosis.

If the pancreatic ferments play so important a part, even under aseptic conditions, we can readily understand their intensified action on the tissues when combined with bacterial infection. That these ferments are really of such importance in the development of acute pancreatitis, is shown by the frequent occurrence of fat necrosis accompanying this disease. The characteristic features of acute pancreatitis are due, therefore, to the action of the pancreatic ferments.

The surgeon has little interest in the nature of the bacterial infection of the pancreas, when the latter is only a part of a general systematic infection. Surgical interference is indicated particularly in those cases in which the pancreatitis is a purely local condition. This, according to our present knowledge, is very often the case. We know to-day, thanks to the researches of Robson,

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Opie and Koerts, that the pancreatic duct, like the common bile duct, is easily infected from the duodenum. The surgeon should always bear in mind that acute and also chronic pancreatitis often follows cholelithiasis and cholangitis, as the infection travels from the bile duct through the ampulla Vateri in a backward direction to the pancreatic duct. Opie has established the fact that a gallstone can be caught in the ampulla Vateri, and close it. Then under favorable anatomical conditions it can produce a retrograde flow of infectious bile into the ductus pancreaticus. Pancreatic calculi can of themselves cause a similar irritation. This, however, in contradistinction to gallstones seldom occurs.

The surgeon will, accordingly, bear in mind the following points in considering the etiology of acute pancreatitis:

1. The very slight tendency of pancreatic hemorrhage to stop spontaneously.

2. The locally destructive and the general toxic action of the pancreatic ferments set free by the inflammatory and hemorrhagic processes, and finally,

3. The ease with which the pancreas may be infected from the ductus choledochus.

If these propositions are correct, I believe that the course of the surgeon, in order to master the situation, is clear.

We may consider acute pancreatitis as an acute phlegmon of the pancreas which, on account of the peculiar nature of the tissue, runs an unusually severe course. As in an ordinary phlegmon, so in the pancreas, the only rational therapy is to open the focus of infection with the knife and to empty and drain the toxic and infectious exudate. Gauze tampons will best combat the fatal tendency to hemorrhage.

Of course, there are different degrees in the intensity of this process, just as in ordinary phlegmon, where we meet the most severe form of general sepsis, as well as the most harmless furuncle. In such cases the surgeon will often refrain from operation when neither the general system nor important tissues or organs in close contact with the infected area, are in danger of infection. But when the infection threatens to spread to vital organs, the surgeon will not dare to rely on spontaneous absorption, or wait for the formation of a typical abscess. He must unhesitatingly proceed to lay open the focus of infection with the knife.

Such considerations, I should think, answer the question as to the expediency of surgical interference in the first,—the most acute

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stage of pancreatitis. We should not in general allow the severe symptoms to pass and delay the operation until the formation of an abscess.

To continue the comparison between acute pancreatitis and acute phlegmon, we can hardly conceive of a region in which the focus of infection could be more unfavorably placed. Not only is the patient threatened with severe toxic and general septic symptoms, but he is also exposed to the danger of a progressive general peritonitis. This is especially likely to develop in the subphrenic space, giving rise to subphrenic abscess. There is also the danger of formation of a phlegmon in the loose tissue of the retroperitoneal region which is rich in lymphatics. From this, again, other complications arise, such as pyaemia, a phlebitis or even a pleurisy. Most surgeons, even at the present time, are more or less opposed to early operation in acute pancreatitis, and clinical experience seems to justify their disapproval, for the results of early operation are not as good as those which follow later surgical interference.

Of the cases I have collected, only 9 out of 46 operated upon in the acute stage recovered. On the contrary, 18 out of 35 recovered when the operation was done during the later stages of the disease. I believe, however, such statistics are of no great value.

First of all, we do not know from statistics available at present, how many of these patients with acute pancreatitis really survive the acute stage, and go on to the subacute, the most favorable stage for operation. I believe that comparative statistics in this regard will show that the great majority of the patients die in the acute stage. The possibility that a goodly number could be saved by means of a rationally conducted early operation can not at the present time be denied. I say purposely "a rationally conducted" operation, for the operations done up to the present time for acute pancreatitis were not all rational procedures. As we know, most cases have been operated upon under a false diagnosis, and the disease has not even been recognized at the time of operation, the surgeon being compelled to close the abdomen without having relieved the condition of his patient. The post-mortem examination in these cases has first shown the true condition. The operation was usually done, a diagnosis of perforative peritonitis or intestinal obstruction having been made. The suspected perforation or occlusion was looked for; the operator thoroughly explored the abdomen; in many cases the intestines were eventrated, and finally

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the abdomen was again closed. As a rule, an anaesthetic had been given the patient. It is certain that by such procedures the patient was greatly harmed and not at all or very little helped. The evacuation of the hemorrhagic peritoneal exudate alone was of some value.

Only in recent years, since surgeons have learned to recognize the ominous symptoms of fat necrosis and to refer them to an affection of the pancreas, they have ceased to make a thorough search among the abdominal viscera. Most surgeons to-day still close the abdomen when they have satisfied themselves of the existence of fat necrosis, in the conviction that the patient cannot be saved. Only a few surgeons are in favor of active and direct interference with the pancreas.

Nimier has proposed incising the pancreas in acute pancreatitis and introducing a tampon. Later on, Robson recommended early operation, making a small incision below the umbilicus, and if necessary, a counter-incision at the border of the ribs for thorough drainage. In a similar manner, Lund recommends an incision above the umbilicus, splitting the gastro-hepatic ligament, and thus securing free drainage of the omental bursa. When necessary, the vault of the diaphragm may be exposed, and drained by resection of the tenth and eleventh ribs.

I fully agree with these surgeons, for the reasons which I have previously mentioned. We should, at least, try such methods before admitting that we are powerless in all cases of acute pancreatitis.

The indication for laparotomy, in these cases, is more readily found by the surgeon, as he cannot in any given case make the differential diagnosis between an acute pancreatitis and other diseases calling for surgical intervention, such as acute perforative peritonitis and acute intestinal obstruction. He must in all such doubtful cases think of the possibility of acute pancreatitis. He will be able to make his diagnosis after opening the abdominal cavity and finding a hemorrhagic exudate, upon determining the presence of fat necrosis, and by manual examination of the pancreas.

Having assured himself of these conditions, he should then proceed systematically, instead of terminating the operation at this time, as was formerly done. Cases of this kind, however, offer great difficulties, and we have yet to learn by experience which procedures will produce the slightest amount of surgical shock in the much-enfeebled patient, while still accomplishing the object for which they were undertaken.

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In this connection, I will mention a case of Hahn's,[1] in which that surgeon made an incision below the umbilicus, using local anaesthesia, and after diagnosing an acute pancreatitis, confined himself to merely evacuating a large hemorrhagic exudate and draining the abdomen with iodoform gauze. The fortunate issue in this case should encourage us to imitate this procedure in all those cases in which, owing to the weakened condition of the patient, it is inadvisable to explore the pancreas itself.

But Hahn's case is not the only one of its kind. As early as 1889, Halsted observed a recovery in a case of acute pancreatitis with fat necrosis of the omentum and mesentery where only a laparotomy and removal of peritoneal exudate was done. The operation was undertaken in the belief that the case was one of acute intestinal obstruction. Four years after operation a similar attack occurred in this patient.

Another case was operated upon by Pels-Leusden in 1901 in König's clinic under similar conditions and with a successful result. The peritoneal cavity was drained.

Finally, Henle, three years ago, operated upon a case in my clinic, in which the diagnosis of acute intestinal obstruction had also been made. After demonstrating the presence of an extensive fat necrosis in the omentum, a large peritoneal exudate was removed. An artificial anus in the caecum was established to relieve the condition of intestinal paralysis. The patient recovered and the artificial anus was closed six weeks later. In the course of the following year similar attacks recurred, but these were always less severe and subsided after high enemata.

This small number of favorable results does not allow us to draw binding conclusions regarding the efficiency of these operations. One could infer that the patients recovered not because of, but in spite of the operation. I believe, however, that even at the present time the following can be stated in favor of surgical interference:

1. The operation according to Hahn, under local anaesthesia, can be performed so easily, that we can employ it even in collapsed patients without running any great additional risks.

2. Emptying of the peritoneal exudate and thorough flushing of the abdominal cavity with a 0.9 salt solution, is surely of great benefit to the patient, more especially when the peritoneal cavity is later on drained.

[1] Deutsche Zeitschrift f. Chir., Vol. 58, page 1, 1901.

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3. An artificial anus, according to Henle, should be established only when intestinal paralysis exists.

Whether or not we will in future secure such favorable results with the methods already in use, as were obtained in the four cases of Halsted, Hahn, Pels-Leusden and Henle, further experience alone will show. It must particularly demonstrate whether the simple operations, which do not directly include the pancreas itself, are sufficient not only to remove the symptoms of intoxication, but also to check the further development of the disease. *A priori,* one must consider an incision into the pancreas followed by drainage as a rational treatment in acute pancreatitis, even as in an acute phlegmon we make deep incisions to remove tension and expose the focus of infection, or as we open the medullary canal by trephining in the severe septic forms of osteomyelitis before the formation of real pus. The statistics up to date, in spite of these four favorable cases, as far as we may judge, show that an operation which does not disturb the pancreas, favorable as its influence may be on the general condition, does not help materially in combating this terrible disease.[1]

By active interference in the acute stage, we not alone desire to overcome the septic condition to which most of the patients succumb, but also to ward off necrosis and sequestration of large portions of the gland occurring in many cases. Even should the surgeon be able to remove the disintegrated portions of the gland, the loss of a considerable amount of pancreatic tissue might prove a serious matter to the patient later on. Among the cases of pancreatic necrosis which have been operated on with a favorable result, we find many in which the patients have succumbed to increasing emaciation and pancreatic diabetes from a loss of function of the gland.

So far I have considered only the cases of acute pancreatitis and, speaking generally, I have ventured the opinion that they should be subjected to surgical interference. As I have already stated, this seems to me eminently proper, as a differential diagnosis between acute pancreatitis and other diseases, which also demand immediate laparotomy, is hardly possible.

We must judge the *subacute* forms of pancreatitis somewhat differently. Cases occur in which the first fulminating attack dis-

[1] I have collected 75 operations for acute pancreatitis, which were performed in the early as well as the late stages of the disease. Of 37 cases in which the pancreas was involved in the operative interference, 25 recovered; in 41, where the pancreas was not touched, 4 cases recovered (the cases of Halsted, Hahn, Pels-Leusden and Henle).

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appears rapidly, or in which the disease begins insidiously at the outset, only gradually developing severe local and general symptoms. Here the surgeon has time to observe his case more carefully, and to consider the advisability of combating the attack without surgical interference; indeed, a delay in most of these cases is not inopportune, as the diagnosis is still more uncertain than in acute pancreatitis.

Chronic inflammations of the pancreas were not regarded as suitable for surgical treatment until a short time ago.

It was first shown by the observations of Riedel, Koerte, Lancereaux and Hardin, and more especially by the careful work of Robson, Halsted and Opie, that cases of chronic pancreatitis, which otherwise had seemed hopeless, were not only improved, but also completely cured by operative means. We have learned two things, above all others, in the last few years: first, that chronic pancreatitis runs a course not dissimilar to that of pancreatic carcinoma and has often been mistaken for the latter, and, second, that active interference has often been postponed because we have been unable, as just stated, to properly recognize the condition of chronic pancreatitis, and have confounded it with a condition beyond surgical relief. It is easy to understand how the clinical symptoms of both affections, especially in disease of the head of the pancreas, could show a resemblance. But even after opening the abdomen, the differential diagnosis can often not be made by palpation, since in both cases the diseased portion of the pancreas presents a hard, irregular mass enclosed in the gland. Only recently, in a case of that nature, with closure of the common bile duct by the indurated head of the pancreas, I did a cholecyst-entero-anastomosis in the belief that I was dealing with a carcinoma. When the patient died ten days later of pneumonia, I learned from a microscopical examination that I was dealing with a case of chronic pancreatitis. In several other cases, during my earlier experience, I have made a diagnosis, with or without operation, of carcinoma of the pancreas, and have in consequence given an unfavorable prognosis. In these cases the patients have recovered. The diagnosis should, of course, have been chronic pancreatitis.

Another no less important point, to which Koerte, Robson and Opie have called attention, is the close relation existing between chronic pancreatitis and diseases of the biliary tract. Gallstones which become impacted near the papilla Vateri, even though small, have an important bearing upon the development of chronic as well

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as acute pancreatitis. Infection arising from a cholangitis may spread through the pancreatic duct to the pancreas. On the other hand, a chronic pancreatitis of the head of the pancreas can easily simulate a cholelithiasis by compression of the common bile duct.

From what has been said, it is evident that chronic pancreatitis must always be considered in making a diagnosis of cholelithiasis, and further, that with gallstones and cholangitis, especially when the common duct is involved, one must be prepared to find a lesion also of the pancreas.

Barring the cases of chronic pancreatitis already discussed, pancreatic calculi are found only in very exceptional cases.

The surgeon should always bear in mind the possibility of a pancreatitis developing as the result of a chronic intoxication (alcohol) analogous to the development of cirrhosis of the liver.

Owing to the uncertainty of the diagnosis of these conditions, an operation should always begin as an exploratory incision. Only after establishing the diagnosis on a firm basis, by local examination, is the surgeon enabled to further develop his plan of operation. He must choose between two ways: he must strive to remove the cause of the disease; this he will do when he finds impacted concretions in the common bile duct, the papilla Vateri, or Wirsung's duct. The technique of all these operations is not unlike that of cholelithiasis.

As impacted calculi generally give rise to an infectious cholangitis, or an inflammation of the pancreatic duct, drainage, as a rule, of one or both ducts must be provided. One should also drain the neighboring portions of the peritoneal cavity with tampons.

The second way is more indirect, inasmuch as only a free outlet for the confined and infected bile is established. This can be done through a gall-bladder fistula by means of a cholecystotomy when the cystic duct is free, or by establishing a communication with the small intestine by means of a cholecystenterostomy. Both operations have their advantages and disadvantages.

The technique of the first is more simple, and does not permit a permanent infection of the bile tract from the contents of the intestine. It has the disadvantage that the patient is burdened for a long time with an external fistula, the closure of which may prove difficult. The question as to which of these two operations is preferable has not yet been answered by clinical experience. I want, however, to emphasize that the importance of a retrograde infection of the bile tract from the intestinal fistula is by no means so great

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as it may at first appear; this, at least, the experimental work of Radziewski, done in my clinic, would indicate.

The danger of infection is greatly diminished when the plan which I recommended in these cases is employed. After cholecystenterostomy an entero-anastomosis is immediately added at a distance of about 10 centimetres from the original anastomosis, which deflects the intestinal circulation from the loop in connection with the gall bladder.

I should also recommend that the surgeon do not hesitate too long in operating for chronic pancreatitis, as severe disturbances of nutrition can occur following gradual degeneration of the organ. Of course, when only mild symptoms are present, one will not resort to the knife at once, but rather recommend internal medication.

The results of operation at present in chronic pancreatitis are very encouraging. If I include 22 cases of Robson, in which there was only one death in connection with the operation, I find 36 cases reported, of which 13 recovered and 5 proved fatal.

One can treat the subject of surgical interference for pancreatic calculi very briefly as they are known to be very rare, and consequently, no very detailed accounts of the experience of surgeons with them are available. I find reports of two cases, both of which died following operation. In one of them the stones were removed from the head of the pancreas and the ductus Wirsungianus. In the second a cholecystentero-anastomosis was done, as a diagnosis of pancreatic calculi was not previously made.

Since a pancreatic stone does not give rise to any characteristic symptoms, and is only recognized as such when passed in the faeces, the surgeon is only concerned with the secondary changes which its presence may cause. These will arise from a blocking of the pancreatic duct or its branches, and will become evident from an accompanying chronic or subacute pancreatitis. The surgeon will find an indication for interference only if symptoms of pancreatitis are present. In all such cases, therefore, we should also remember the possibility of the presence of calculi.

Gentlemen, before retiring in favor of my colleague, Dr. Roswell Park, permit me briefly to give my personal experience in the field of pancreatic surgery. The thirty cases in which I have had the opportunity of operating upon the pancreas while performing a resection of the stomach for cancer, I have already considered.

Besides these, during the twelve years that I have been in Breslau, I have operated on the pancreas 30 times; 10 of these were typical

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pancreatic cysts, of which 2 were removed and 8 were incised and drained. All recovered.

A subacute pancreatitis occurred twice among these cases, once leading to abscess formation and the second time giving rise to fat necrosis. The abscess healed after incision. The other patient was the one before mentioned as the case of Dr. Henle, who was restored to health after a preternatural anus had been established. He was successfully operated upon without disturbing the pancreas. A case of chronic pancreatitis, also previously mentioned, died of pneumonia ten days after a cystentero-anastomosis. In a case which was mistaken by me for carcinoma the patient lived four years after the laparotomy.

In one case of contusion of the pancreas, the result of blunt force, twenty-four days after the lesion, an immense hematoma was opened and drained. The case recovered. This case was also mentioned before.

I have observed 15 malignant growths involving the pancreas. In these exploratory laparotomy was done 7 times and cholecystenterostomy 5 times. Of the latter, 1 died as a result of the operation.

Once a gastro-enterostomy was done for a stenosis of the duodenum due to a pancreatic tumor.

Once drainage for a softened tumor which was taken for a cyst was made, and

Once extirpation of a tumor in the head of the pancreas was done. All three cases ended fatally.

Addendum.—A week after I had read my paper before the Congress at Washington, I had the privilege of seeing a case of acute pancreatitis in the Massachusetts General Hospital in Boston, which had been operated on by Dr. C. B. Porter with an excellent result. In this case, for the first time to my knowledge, multiple deep incisions were made into the substance of the pancreas, to relieve tension, in the manner which I have suggested in the present paper. As this case marks the first practical application of a definite surgical principle in acute pancreatitis, I take the liberty of adding the history as kindly furnished me by Dr. Porter.

S. P., aged thirty-six years, salesman, entered the Massachusetts General Hospital, February 17, 1903, as a patient of Dr. C. B. Porter.

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History.—Patient had previously entered the hospital on October 30, complaining of dull pain in the right hypochondrium for the past seven years, and chronic constipation. A year ago he was seized with sharp pain in the epigastrium, which later localized itself in the right iliac fossa. The pain was constant and very severe. No vomiting, no chill; had never been jaundiced. Examination at that time showed the abdomen to be tender, especially in the region of the gall bladder, where there was some rigidity. Under rest in bed, in five days the patient was discharged relieved, to report again.

From November 5 until re-entry on February 17, patient had had several attacks of severe pain in the upper abdomen and right hypochondrium. A month ago he had slight jaundice, and a diagnosis of gallstones was made. On February 15 patient suffered from a sudden and very severe abdominal pain in the epigastrium and right iliac fossa, was nauseated, but did not vomit. Morphine gave relief. Pain continued, and has steadily increased; is now general throughout the abdomen, somewhat more marked in the right hypochondrium and flank. Last night patient began to vomit, and this has become continuous. Bowels moved once after an enema.

Examination showed a somewhat emaciated man, evidently in great pain and distress. Skin was moist, slight dyspnœa. Patient is vomiting continuously, thrashing about in the bed. Vomitus, brown, sour-smelling, not faecal, no blood. Abdomen moderately distended. Greatest pain referred to the right costal border and epigastrium, next to the right iliac fossa. No visible peristalsis. Rigidity moderate. Less marked in the epigastrium and the right iliac fossa. Deep pressure in the latter region causes pain and increased rigidity. Examination of epigastrium impossible, owing to rigidity. Abdomen tympanitic in center, flat in both flanks, dulness shifts readily, therefore free fluid is present. Temperature, 100° F.; pulse, 100, of poor quality; respiration, 30; leucocytosis, 8,000. At the time a diagnosis was made of probable intestinal obstruction from a band in connection with an old inflammatory process about the gall bladder or appendix.

Ether was given, and a median incision from three inches below the ensiform cartilage to two inches above the pubis, through the right rectus muscle. On opening the abdominal cavity, large amounts of brownish red fluid emerged. This fluid was clear, and evidently colored by blood. Culture made reported sterile. The intestines were everywhere injected. No tumor or band could be

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found, and no specially distended coils of intestine. Examination of the appendix showed that it was large and injected, but not gangrenous. Disseminated throughout the abdomen were numerous areas of fat necrosis, which varied in size from a pinhead to a split pea. The fat necrosis in the meso-appendix was especially well marked. The appendix was removed.

Examination of the gall bladder showed a few adhesions, and that it was slightly distended with bile. Examination of the pancreas showed it to be enlarged to three times its normal size, very hard and tense. After thorough irrigation of the abdomen with salt solution, the median incision was closed, and an incision along the left costal margin, five inches long, made. With deep retractors the ribs were held upward, the small intestines and stomach were packed with gauze upward and towards the median line. Examination of the pancreas was made through the mesentery of the transverse colon. From the spleen to the duodenum the pancreas was very large, tense, and oedematous, of a deep purplish color. No stones could be felt in the duct. It seemed evident that the diagnosis of acute pancreatitis required proper drainage, therefore an incision was made through the mesentery from the median line to the tail of the pancreas. This incision was about four inches long and three-quarters of an inch deep. Several areas of fat necrosis were found in the peripancreatic tissue. A rubber tube was placed up to the pancreas, and all of the intestines were carefully walled off with gauze sponges.

Recovery after operation was rapid. Vomiting stopped, the patient had far less pain, there was no fever, no increase in the white count, and the pulse soon fell to 80. At the end of a week the gauze was changed, and the wound appeared healthy. On the twelfth day two small pieces of gangrenous fat tissue came away. The gauze was changed three times a week, and the wound rapidly granulated and healed. Throughout the convalescence the leucocytosis never rose above 10,000. There was no distention, the bowels moved normally.

Urinary examination showed interesting conditions. Immediately after the operation, a slight trace of albumen, with granular casts. On the 23d of February bile in large amount, few casts, also 1.4 per cent. of sugar. On the 26th sugar was absent, albumose present in small amount. By March 2 the urine was normal, except for an increase of indoxyl and kreatinin. Numerous experiments were made with salol, feeding with a large amount of grape sugar, etc., and investigation of the stools for undigested fat. All of these tests showed nothing abnormal.

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On April 1 the patient was up and about, and had gained much in color and general health. Convalescence seemed perfect.

About the middle of April, however, he complained from time to time of pain in the epigastrium, above the umbilicus. There was no fever, no increase of leucocytosis. The bowels had not been acting very well.

In view of the persistence of this pain, it seemed wise on April 17 to operate again, in order to find out whether a stone was impacted in the common duct, and if none were found it was planned to drain the gall bladder. On April 17 a five-inch incision was made along the outer border of the right rectus muscle, from the rib margin downward. On opening the cavity, adhesions were discovered between the omentum and the anterior abdominal wall. The gall bladder was found to be much thickened, but not distended. Numerous adhesions about it showed evidence of an old inflammation. The duodenum was separated from behind; with one finger in the foramen of Winslow and another behind the duodenum, the whole biliary passages were examined. No stones could be felt, but the common, cystic duct, and gall bladder were markedly thickened. The pancreas had again resumed its normal size and feel, except in the head, where some induration was present. No evidences of fat necrosis had remained behind. Finally, it seemed best to make a small incision by tearing between the stomach and the transverse colon. With one finger in the lesser peritoneal cavity and the others behind the duodenum and pancreas, careful palpation revealed a slightly fluctuating area in the head of the pancreas, about two centimetres in diameter. This was incised through the lesser peritoneal cavity, and a teaspoonful of broken-down débris evacuated. Cultures from this were sterile. A fingertip placed in the cavity could feel no stone. This cavity was curetted clean and packed with gauze. The gall bladder was sewed to the anterior abdominal wall, but not opened. A wick was inserted under it to drain the space rooted up by the freeing of the duodenum.

Convalescence from this operation was complicated by pneumonia in the right base, with much foul, purulent sputum. The temperature rose to 103° F., but fell to normal six days after operation, from which time convalescence has been uninterrupted. On May 20 the patient was discharged with a very small sinus in the wound. Owing to freedom from pain, the gall bladder has never been opened. No sugar or abnormal urine constituents could be found after the second operation. Patient has gained ten pounds in weight.

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THE PANCREAS AND PANCREATIC DISEASES.

THE SURGICAL CONSIDERATION OF CYSTS AND OTHER NEOPLASMS OF THE PANCREAS.

BY ROSWELL PARK, M.D., LL.D.,

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For many centuries and until comparatively recently, the profession were in absolute ignorance of the nature and function of the pancreas. To be sure, Wirsung had described its principal duct in 1642, after which discovery it came to be regarded as an unimportant internal gland with some sort of a secretion. The first epoch in its modern history was marked by the experimental researches of Claude Bernard, during the earlier decades of the last century. Another occurred many years later when Langerhans described the peculiar structures or portions of the gland which now bear his name. When Fitz described for us, in this country at least, the acute lesions of this "internal spittle-gland," as the Germans call it, he created the third epoch, and the fourth epoch began when Gussenbauer first, in 1882, showed how it might be surgically attacked.

The amount of study of the pancreas and the wealth of recent literature concerning it may perhaps best be gathered by comparing the brief article in Ziemssen with the long monographs of Oser, Robson and Moynihan, Körte and Truhart. The fourteen hundred different titles given in Oser's bibliography, in the recent American edition of Nothnagel's System, will serve to show the richness of our present library facilities, while the difficulties with which we still make diagnoses of pancreatic lesions will indicate the fact that many of them have been written to, as yet, little purpose.

The materials for an essay on csyts and other neoplasms of the pancreas have been nearly exhausted, and until more experience has accumulated we shall have to simply thresh over what has been already placed before us. Our knowledge is much less complete than it would be were not these lesions rare in animals and seldom met with at autopsy. At present the existence of a suspicious tumor in the upper abdomen would lead to an operation in almost every case, where, if it were not operated, an autopsy would be permitted. And so, while the patient is benefited by the operation, the surgeon has only the somewhat meager opportunities of seeing the tumor, in its fresh state, to be sure, but through a very limited opening.

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The surgeon who finds a cyst which he considers to have its origin in a pancreatic lesion, will deem it for his patient's interest to so deal with it as to cure it, and not to make an autopsy *in vivo,* and so therapeutic considerations become paramount and pathological inquisitiveness must be suppressed.

I gather from a recent paper by Rickets, that in 1730 Behn tried to cure a pancreatic cyst by injecting into it a solution of nitrate of silver, and that in 1857 Parsons reported a case of pancreatic cyst due to obstruction of the duct. A number of years before this, i. e., in 1789, von Doeveren reported a case of cancer of the pancreas, while sarcoma as such was first recorded by Paulicki.

Anatomical considerations—Aside from the gross anatomy of the pancreas, it is worth while for the surgeon to remember the anomalies that may possibly be met with in this region, which he may at any time have to encounter, and which might confuse or confound him. These may include:

1. Complete absence of the pancreas, which has been reported as totally lacking in at least one case.

2. Abnormalities of the ducts, of which either one may be absent, or which may empty independently into the duodenum. The duct of Wirsung may be double, or there may be even three excretory ducts, as in the chicken and pigeon. In 56 of 105 specimens examined by Schirmer, the duct of Santorini passed from the main duct into the duodenum, opening on a papilla an inch above the common duct. In 19 it did not open into the duodenum at all, while in four cases it formed the only pancreatic duct. (Huntington, *Anatomy of the Human Peritoneum and Abdominal Cavity,* page 114.) When the duct of Santorini does open into the duodenum it may take the place of the regular duct, as when the latter is obstructed by gallstones.

3. One might possibly meet with that form of annular pancreas first described by Ecker, where the descending portion of the duodenum is surrounded or encircled by a band of pancreatic tissue continuous with the body of the pancreas. This portion may have its own duct. Constriction of the gut may be thus produced at this point with dilatation of the part above. At least six cases of this character have been recorded. They remind us of the earlier form of the pancreas when it was largely concealed within and scattered along the intestinal walls and folds of the mesentery. The pancreas may also be divided into two almost separate parts connected by the duct, or it may have an accessory lobule springing from its head and extending anteriorly along the duodenum.

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4. An accessory pancreas may also be met with. Ruediger has recently collected twenty such cases, of which five were located in the stomach, two in the duodenum, nine in the jejunum and four in the ileum. Three of these were associated with diverticula. (*Jour. of the Am. Med. Assn.*, April 18, 1903, page 1059.) These may possibly give rise to intussusception or even to carcinoma. (Nicholls, *Montreal Med. Jour.*, 1900, Vol. 29, page 903.) They remind us of the pyloric caeca or appendices met with in many of the fishes and so well described by Huntington. Each accessory lobe, if large, may have its own duct.

CYSTS—Oser has been able to collect 134 cases of cysts of all kinds. It seems wise to adopt Robson and Moynihan's classification of these lesions, because it is "as precise as our present knowledge permits."

1. Retention.
2. Proliferation.
3. Hemorrhagic.
4. Hydatid.
5. Congenital.
6. Pseudo cysts:—Peri-pancreatic.

1. *Retention cysts* were described by Virchow in 1863, as consisting of two varieties,—one form including a botryoidal dilatation of the duct of Wirsung, the other being due to obstruction of the outlet with expansion of the entire canal into cystic outlines, which may attain the size of an orange, and contain mucoid, bloody or calcareous material. This latter form rarely attains a size great enough to require operation. To these types Klebs added a third, originating in the smaller ducts, possibly even in the alveoli, to which he gave the name "acne pancreatica." These are found usually in groups, the larger being formed by coalescence of smaller cysts. The causes of these retention cysts are:—

Intrinsic.	Impaction of calculi. Stricture.
Extrinsic.	Pressure from without. Abnormalities of shape or position. Closure or obstruction by parasites.

Impaction of calculi includes gallstones occluding the opening of the common duct in the ampulla of Vater (which may cause chronic pancreatitis, as well as cystic expension), and pancreatic calculi

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which may be found at the termination of Wirsung's duct or along its course.

So far as stricture is concerned, it may be found anywhere along the duct. It may be due to healing of a duodenal ulcer, since Perry and Shaw have collected four instances of this kind; or, it may be produced by a chronic lesion, or by the friction and abrasion of a calculus, or by the repair following a traumatism. In rare cases both the biliary and pancreatic passages may be distended from a terminal stenosis or pressure. By Tilger and by others the most common causative factor is thought to be some sclerosing process, with or without such retrogressive metamorphosis of epithelium as permits auto-digestion of the gland by its own juice with the resulting formation of a cavity. There are certainly enough cases on record to justify this view, and henceforth chronic pancreatitis must be recognized as the commonest cause of retention cysts by occlusion of the duct.

That the mere closure of the duct is insufficient, occasionally if not invariably, was proven by those earlier experimenters who showed that ligation of the duct is quite insufficient to produce more than a trifling distention of its lumen, the pancreatic secretions being absorbed after the intra-canalicular pressure attained a certain degree. Mere mechanical occlusion, therefore, is only a minor factor in this cyst production, something beyond this being at fault. Heinricius finds this fault in a diminishing or disturbed absorption of pancreatic juice, due either to some admixture with non-absorbable and abnormal substances, or to a lack of function on the part of the absorbent vascular system.

Of the extrinsic causes pressure from without may be produced in ways rather too numerous to recount, including tumors variously placed or originating, calculi, etc.

Abnormalities include relaxation of the pancreatic supports, permitting ptosis or dislocation of a part or the whole of the gland, displacement by adhesions or growth of tumors, cicatricial retractions and those congenital anomalies to which attention has already been drawn. Occasional instances of these retention cysts are seen during autopsies. To certain of them Virchow gave the name of "pancreatic ranulae." They have also been met with unexpectedly during intra-abdominal operations not meant for their particular removal. I fear that hereafter few operators will be able to resist the temptation to attack such cysts should they be thus revealed to sight and prove operable; nor, in the light of our present knowl-

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edge is there any good reason why, when thus recognized, their removal or marsupialization should not be undertaken, the patient's condition otherwise justifying it.

So far as the obstruction of the duct by parasites is concerned, it must be remembered that lumbricoid worms have been known to pass from the duodenum into the duct of Wirsung and there cause obstruction, or by their death cause infection. At least two such cases are on record, Durante having reported one of them.

2. *Proliferation cysts*—These may sometimes evince malignancy, many of them being so close to the border line between proliferating cystoma and cystic carcinoma that only the subsequent course of events would indicate on which side of this line they belong. They are really neoplasms comparable to certain cysts in other places. They comprise cyst-adenoma, of which Cumston has not been able to find reports of more than fifteen cases. (*Annals of Surgery,* February, 1902, page 230.) These are cystic, glandular tumors, multilocular, lined with cylindrical epithelium, sometimes forming crypts and sometimes polypoid proliferations. Some of them seem to be independent of the excretory ducts. They occur near the tail rather than near the head of the pancreas, and their contained liquid is often blood-stained. Some writers believing that these cysts are really of hemorrhagic origin, have called them *apoplectic cysts,* reasoning that hemorrhage is the result of a passive hyperaemia, which itself is the consequence of a chronic interstitial sclerosing process; nevertheless, these are not blood cysts in the sense that they result from bleeding into a pre-existing cavity. Other writers, Tilger especially, believe that the interstitial contraction of the smaller vessels obstructs secretion and that this leads to formation of minute cysts, which slowly enlarge because of the peculiar character of their contained secretion, their septa being digested away and larger cysts being thus formed, the argument being that the absence of the fibrin-digesting ferment shows that it has been used up in this process. But this ferment is not always absent; sometimes it is the fat or the starch-digesting ferment which is missing. The truth is that the pancreas is so protected from hemorrhage that most of the conditions which affect it proceed toward it from the stomach or biliary passages, and the conditions which may lead later to a chronic interstitial pancreatitis are numerous; nevertheless, traumatisms are not without their influence, and observations such as are needed to clear up this question have as yet been few in number.

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Under the head of *cystic epithelioma* have been described cases of what were probably better called cystic carcinoma. It should be said that these are essentially cystic formations with cancerous deposits in their walls, perhaps multilocular, usually accompanied by secondary growths in the liver or adjoining tissues. The latter probability would make most of them inoperable.

3. *Hemorrhagic cysts*—Here we must distinguish between a hemorrhage into a cyst and a true apoplexy of the gland with resulting cystic degeneration of the clot. Most cysts containing blood belong to the former, i. e., are retention cysts into which blood has escaped in varying quantity. Those to which the term apoplectic can be best applied attain often considerable size, like Gussenbauer's historic first case, are usually solitary and occupy the left end of the pancreas.

4. *Hydatid cysts*—These are exceedingly rare. Oser does not mention them. Tricomi says seven cases are on record. Moynihan mentions a case each of Graham, White and Peters. We may, therefore, dismiss these with but curt mention. The Briggs case of sarcoma successfully removed proved to be an echinococcus cyst which had undergone sarcomatous degeneration.

5. *Congenital cystic degeneration* resembles more or less that of the other solid viscera. Moynihan mentions but three of these instances. The condition is probably not one which permits of surgical relief, although it might seriously perplex an operator, should he come upon it.

6. *Pseudo-cysts,* as Körte has proposed to call them, constitute a large proportion of cases reported as pancreatic cysts. These are collections of fluid in the lesser omental cavity or bursa, which sustain such intimate relations with the pancreas as well as other viscera,—even containing pancreatic elements,—that it is impracticable or even impossible to distinguish between them and the true forms above alluded to. They can also be spoken of as peri-pancreatic cysts; doubtless cysts of the adrenals or even of the kidneys have been thus mistaken.

Of these as a class it must be said that they have very much to do with the pancreas, being the result usually of injury to that viscus. The escape of blood into the lesser cavity of the peritoneum, followed by that of pancreatic juice, may very easily produce a tumor which, in the living subject, it may be impossible to distinguish from a true cyst. Lloyd has insisted that the fact that a cavity within the abdomen contains pancreatic secretion is no proof

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that we are dealing with a pancreatic cyst, but merely that it is connected with the pancreas; nor is it enough to feel the pancreas when the examining finger is introduced through an incision, for if the lesser peritoneal cavity is opened through the transverse mesocolon, the finger will enter a large cavity at the back of which the pancreas should normally be found. This cavity varies in capacity in different individuals, as Moynihan has shown. It lies in front of the pancreas, is closely adherent to it with no intervening fat, even in the most obese. If opened through the great omentum, close to the lower border of the stomach, it appears to be arranged in three compartments. Effusion into it must produce a tumor strikingly resembling a true pancreatic cyst. Lloyd is doubtless right in holding that contusions of the upper abdomen may be followed by development of a tumor in this region due to fluid accumulations in this lesser peritoneal cavity, whose fluid contents may be able to rapidly convert starch into sugar, and that these have too often been regarded as true retention cysts of the pancreas. He holds, furthermore, that a diagnosis of this condition can usually be made by the characteristic shape of the swelling,—it occupying rather the umbilical, epigastric or left hypochondriac regions,—as well as by the absence of trypsin.

Moynihan has quoted the case of MacPhedran, who found a pseudo-cyst in a man of 53, at the bottom of which lay the pancreas, enlarged but firm, covered by healthy peritoneum. Five months later it became necessary to open the abdomen again because of another tumor, which this time was found to be a true pancreatic cyst, whose fluid possessed digestive properties. Mistakes have also arisen by dealing with such cases as effusions in the greater or lesser omentum, or in the walls of the stomach or colon, as well as in the case of retroperitoneal collections of fluids, many of these lesions being due to traumatism. Some of these pseudo-cysts form very rapidly and thus, as it were, "tell on themselves." Others come on very slowly and produce distress in the epigastrium. The more rapid the growth the less likely that the pancreas is primarily at fault. The injury which causes the hemorrhage may also be followed by an adhesive peritonitis, which may limit the accumulation and even close the foramen of Winslow, and so a cyst may form between the stomach and colon. It appears likely that injury has more to do with pseudo-cysts and morbid processes than with the true pancreatic cysts. It appears that the greater proportion of the former are met with in males, who are more exposed to injury, whereas of the latter the majority seem to occur in women.

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For reasons already given pancreatic cysts are met with oftenest in men. The youngest case is recorded by Shattuck, aged 13 months. Richardson operated upon a case 14 months old, and Sliéda one of 76 years. The body of the pancreas is most commonly affected. The cysts may be single or multiple, ranging from the smallest up to 20 liters or more. The contained fluid may be of almost any color, but is usually brown, tinted according to the amount of blood admixture. It is alkaline in reaction and of low specific gravity. It always contains albumin, usually cholesterin, and sometimes various epithelial or fatty debris. It may contain either of the pancreatic ferments, proteolytic, fat-splitting or starch-converting. The latter seems unimportant, the two former of interest, even of importance. Their presence is of real import, their absence of negative value. When enzymes are present in considerable and active amounts the presumption is strong that this fluid comes from the pancreas.

In rare cases the tumor is movable. When the growth is large, reaching into the pelvis, an ovarian tumor may be suspected. In one case of my own where I wavered as between hydronephrosis and pancreatic cyst the tumor proved to be an ovarian cyst of one side, pushed up from below by another on the opposite side. The cyst wall is commonly quite vascular and there may even have occurred changes enough in the surroundings to considerably alter the nature of the original fluid. When lined with original epithelium the granulation process is interfered with and final closure may be exceedingly slow, since a secreting membrane does not readily granulate. In a case of my own final closure did not occur for seven or eight months.

Fistulae resulting from these operations have thus been exceedingly difficult to deal with in many instances. Körte's case discharged for two years and a half and then suddenly closed spontaneously. Murray has reported a case of pancreatic fistula which showed a most interesting phenomenon, i. e., the dependence of transudation upon intravascular pressure and its vaso-motor regulation through the splanchnics, since the secretion was wonderfully influenced by the patient's emotions. (Vide also von Brackel, *Zeit. f. Chir.*, 49, p. 293.)

The growth of these cysts is most commonly beneath the stomach and above the colon, carrying before them the gastro-colic omentum, which, therefore, must be divided in exposing their anterior surfaces. The cases of this character are best suited for operative

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attack, whether by drainage or enucleation. These occur, therefore, on a lower level, tend to press the pancreas downward and, by dragging, to produce a ptosis of the surrounding organs. The next most common direction of growth is above the stomach, between this and the liver, where adhesions would make any attempt at enucleation most grave. These cysts present on a higher level than the others.

These cysts are usually adherent, even firmly or densely so, to the adjoining structures. When thus fixed it will be best not to attempt to enucleate but to drain front and rear. The portal vein has often been found deeply buried in the cyst wall; however adhesions are not always met with and enucleation is sometimes easy. (Cartledge has recently reported complete enucleation of a cyst of the former description, whose firmest attachment seems to have been to the tail of the pancreas. *Jour. Am. Gynaecology,* January, 1903, p. 16.) The genuine pancreatic cysts are least likely to be adherent and the pseudo-cysts most so; still, no *a priori* conclusions can be drawn in this regard.

The symptoms are mainly those caused by pressure and are usually absent until this pressure begins to make them prominent; especially pain toward the end of and after a meal, perhaps with vomiting, usually confined to the upper abdomen, radiating to the left side of the back and left costal arch, varying in intensity from indigestion to violent colic. Vomiting is usually proportionate to the pain. The vomitus is often clear and colorless—the so-called pancreatic salivation of some writers. The other symptoms are vague; emaciation is usually rapid and patients "age" quickly. Fat in the stools and glycosuria when noted are most suggestive, though less frequent in cystic than in other pancreatic diseases, because the whole organ is rarely involved. This is true also of the presence of undigested muscle fibres. Sahli's test may be of some service in these cases. This is based on the fact that the presence of the pancreatic secretion in the intestine causes the decomposition of salol in the duodenum into carbolic and salicylic acids, which may be recognized in the urine. When not found there the assumption is that the pancreatic juice is not being discharged as it should be.

These tumors may present above the stomach, below it and between it and the colon, below the colon, or behind them both, as the diagrams given by Oser and Robson and Moynihan graphically indicate. Usually the stomach is pushed up and to the right, the colon downward. To reach it the parietal peritoneum, the two layers form-

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ing the great omentum and the layer of the lesser sac have to be perforated. The colon may be pushed downward several inches. When the tumor presents above the stomach the gastro-hepatic omentum must be traversed. The protrusion of a cyst through the foramen of Winslow and into the greater peritoneal cavity has been noted. The splenic vessels have been found both in front of and behind the tumor and the superior mesenteric vessels have been known to cross the tumor surface. These tumors lie usually between the umbilicus and the left costal border, though often they are medianly placed. Finally, they may almost fill the abdomen. The larger they are, the more evident their cystic character; the smaller they are, the more easily may they be mistaken for solid tumors. Aortic pulsation is often transmitted; the percussion note will depend, in the location, upon the position of the stomach and colon.

In general, the symptoms and signs depend upon the size of the growth. These may be modified by bursting of a cyst with its sudden collapse, and perhaps refilling, or by hemorrhage into the cyst with a sudden enlargement. It may burst into the peritoneal cavity or into the bowel. In either event this accident may or may not kill. Sudden collapse and pain mean probably a hemorrhage into the cystic cavity.

To puncture such a tumor for diagnostic purposes is to introduce elements of danger which would best be avoided, nor does it give certain knowledge. A tumor of this character which would suggest exploratory puncture is one in which the abdomen should be opened, at all events.

Diagnosis has to be made generally from

1. Local peritonitis with fluid accumulation.
2. Cholecystitis and distended gall bladder.
3. Hydronephrosis and other fluid tumors of the kidney.
4. Ovarian cysts.
5. Hydatid and other cysts of the liver.
6. Adrenal cysts.
7. Mesenteric cysts including cysts of Müllerian and Wolffian remains in the mesocolon.
8. Omental cysts.
9. Splenic cysts, hydatids, etc.
10. Cysts of the stomach wall, which have, in at least two cases, closely simulated pancreatic cysts.
11. Retro-peritoneal lymph and other cysts.
12. The pseudo-cysts above alluded to.

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It does not seem necessary in this place to go into the differential diagnosis of these various lesions.

Operative treatment—There is no treatment for these cases save that by operation. This must consist of

1. Aspiration,
2. Drainage or marsupialization, or
3. Enucleation or extirpation.

1. Aspiration has nothing now to commend it, even for diagnostic purposes. As Moynihan says, "it is redolent of mediaevalism." It has never been successful, since the cysts always refill if simply emptied. There is a theoretical value attaching to the method, which, so far as I know, has not proven real; that is, the possibility of carrying the patient over a crisis of pressure or glycosuria and thus preparing him for radical operation.

2. Choice of location of incision must depend on the point at which the tumor most prominently presents. The old method of Volkmann is essentially that applied to these cases to-day. The coverings of the cyst must be gently perforated, preferably after some portion of the cyst wall has been sewed to the edges of the incision; but before thus attaching it manual exploration should be practiced in order to determine immediately the matter of its possible enucleation, as well as its anatomical identity and relations. For thick-walled cysts the instruments used in seizing and tapping ovarian cysts may be advantageously used. Stitching should be secure and is best done perhaps with silk. After thus anchoring a cyst, but not before, it may be freely opened, but the site of the opening should be free from vessels. It is rarely necessary to do this *a deux temps,* the contained fluid being easily kept out of the general peritoneal cavity, unless the cyst wall be extraordinarily thin so that it is inadvertently ruptured.

Posterior drainage will prove a time-saving measure in many of these cases, so far as final recovery is concerned. This is usually made at the left costo-spinal angle. Among the precautions and preparations for all of these operations *careful cleansing and scrubbing of the patient's back should be included,* so that this posterior opening may be made without delay when it is indicated. (The writer has already reported a case of gunshot wound of the stomach where posterior drainage was successfully made and where this precaution was taken before the operation. See *Annals of Surgery,* 1902, 36, p. 223.) A stab wound which may be dilated with forceps is sometimes enough for this purpose, but must be enlarged so that

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the drain, of tube or gauze, may not be too tightly constricted. It can be made most easily with the left hand in the abdomen as a guide, which should also identify the kidney or the pancreas as well as push them aside. While anterior drainage should be made with a glass or rubber tube, or with a gauze wick, the posterior drain must be of flexible material.

When the cyst is small it may be difficult to attach it to the anterior incision. In this case there must be plenty of packing around the principal drain or a purse-string suture may be used to hold the opening firmly around the tube. This would be preferable if it may be employed. Should this be impracticable, the cavity may be simply packed with gauze which is led out of the abdominal wound, in which secondary sutures should be introduced.

Some anomalous cases have arisen requiring especial and ingenious treatment and deserve mention. Thus Hogen (*Archiv. f. klin. Chir.*, Vol. 62) has reported the case of a boy of thirteen with a cystic tumor, the size of his head, located posteriorly to the stomach and so firmly surrounded by adhesions that it was impracticable to reach it directly and impossible to bring it near the surface. In this case he opened through both walls of the stomach and emptied the cyst. Then he found it possible to bring its anterior wall into contact with the parietal peritoneum by displacing the stomach. After this he closed both wounds of the stomach. Even then it was necessary to exsect a part of the ninth and tenth costal cartilages in order to let the abdominal wall drop down to a lower level. This case recovered.

Peters (Moynihan) opened a hydatid cyst of the tail of the pancreas by cutting down directly from the loin, incision being parallel to the last rib, as for nephrectomy. The lumbar fascia was opened, the colon pushed forward with its peritoneum, and the cyst thus reached retroperitoneally.

Robson collected 84 cases of pancreatic cyst. Ransohoff in 1901 (*American Medicine*, July 27, 1901) had gathered a total of 159 cases of pancreatic cyst subjected to operation. Of these 17 were of the type of cyst-adenoma. This relation may be even more frequent than 1:9 as above. These cyst-adenomata are the most slow growing of all and the least painful. Of these 159 cases all but 34 were sewed to the abdominal wall and drained, with but five deaths. In 12 cases the operation could not be completed; 4 of these died. In 23 cases total enucleation was made with two deaths. At least 20 other cases have been reported since Ransohoff collected

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these statistics. Two of Robson and Moynihan's 84 cases died subsequently of glycosuria, and two others had extension of malignant disease.

The matter of fistula following marsupialization is so important that I think it well to allude to it again, as showing what may happen. Murray has reported a pancreatic cyst in a young woman of 19, in whom a fistula at that time had persisted for three years or more, who wore a rubber tube for one year and after that a small silver tube. During the latter part of this time the secretion or discharge was but very slight save when she became excited or nervous, when it greatly increased. Chemical examination showed this to be a simple transudate with specific gravity often as low as 1003, devoid of elements indicating tryptic proteolysis (*American Medicine*, 1902, July 26, page 133). In this connection it may be remarked that Körte had a fistula stay open for two and a half years and that Gussenbauer has found a specific gravity of pancreatic fluids as high as 1610.

In general, experience has shown that after operation on pancreatic cysts recovery may be prompt and satisfactory and pancreatic function be apparently undisturbed. It is also shown that pancreatic fistulae may persist for a long time without apparent detriment and may be expected to close with or without treatment after a somewhat indefinite period.

Solid Tumors—From the statistics of Remo Segrè, Biach, Oser, Rohde, Soyka, Hale White and others, one may study the records of some 53,000 autopsies, in which only 226 cases of apparently primary malignant disease of the pancreas were found. I say apparently primary, because doubt has been expressed about the primary character of even some of these. The proportion of cases would certainly not be over 1 : 265 autopsies, perhaps not more than 1 in 400 or even 500.

Cancer is by far more common in the head of the organ, which, like the biliary passages, is most open to infection, more than half of the cases appearing here. It may begin in the glandular epithelium or in the cells of the excretory ducts. Sometimes they attain great size. Terrier has extirpated one as large as the patient's head, which weighed five and one-half pounds. Several times these tumors have been found the size of a foetal head. The duct of Wirsung is compressed in nearly all instances. Courvoisier found it obliterated in 55 out of 66 cases. The duct may be dilated beyond the cancer. The intimate relations and the size of some of these

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growths will explain compression and disturbance of the duodenum, or even of the pylorus. By different observers compression has been noted of the entire stomach as well as of the colon, or of the ureters, portal vein, aorta, vena cava, splenic vessels, superior mesenteric vessels and thoracic duct. By breaking down of these growths perforations in all possible directions may result, including the portal vein, splenic artery and coeliac axis. They are most frequent after the fortieth year.

Secondary deposits occur perhaps most often in the liver, but may be found anywhere or even everywhere, since general carcinomatosis has been reported by Oser. Many of the carcinomata are of the scirrhous type; the softer forms are rare. They include the so-called adenocarcinomata; sarcomata are exceedingly rare.

Symptoms—These may be divided under

1. Those pertaining to the pancreas itself and its functions.
2. Those pertaining to adjoining and related organs.
3. Those indicating dissemination of cancer.
4. The tumor itself.

Of course it is impossible to dissociate these in the study of a given case; nevertheless, they may be considered separately as above.

1. Among the earliest though vague symptoms are digestive disturbances, failure of appetite, discomfort after eating, perhaps eructation, heartburn, nausea or actual vomiting. Not one of these is particularly significant, nor are all of them together. Anorexia, even to loathing for food, is sometimes present; at other times patients eat voraciously without satisfaction. Loss of appetite is evidence of obstruction rather than of cancer, since in a number of cases where cholecystenterostomy was done for obstruction of the duct by pancreatic cancer, the appetite returned. When the pylorus is obstructed by tumors and the stomach becomes dilated, vomiting and other severe digestive disturbances may follow. When the growth has involved the stomach wall, blood may be vomited. Curiously, though the stomach is quite free from disease, there is no free hydrochloric acid in the gastric contents. Fatty stools are noticed occasionally, not usually. Voluminous stools, due to fatty and incomplete digestion, are occasionally noted. This is important and common enough to attract attention as well as to call for it. Should this be followed by jaundice and then by glycosuria with epigastric pain and emaciation, a very probable pancreatic cancer may be assumed. Light colored or bloody stools are not infrequent.

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Pain is a very uncertain feature. When characteristic it radiates around the sides to the back and may be severe. It may simulate the crisis of tabes, but it lasts longer and is often worse at night. It has been spoken of as "coeliac neuralgia." It is sometimes paroxysmal, colicky or anginal. When pain is severe there is accompanying tenderness.

2. Jaundice is an earlier or later feature of these cases, usually later. It is of course first a pressure symptom, but later may be due to disease extending outside the pancreatic limits. The usual concomitants are not lacking, clay-colored stools and high-colored urine. Often a distended gall bladder may be felt. Next comes enlargement of the liver, sometimes regular, sometimes by nodes which can be felt. In some cases a late shrinking due to atrophy of the true liver tissues has been noted. Ascites may result from pressure on the portal vein or involvement of the peritoneum. Meteorism from pressure on the intestine may go on even to the point of producing fatal acute obstruction. Pressure on the vena cava may cause dropsy of the limbs, or on the ureter a hydronephrosis. Sahli's test may be also resorted to by giving salol and testing the urine for salicylic and carbolic acids. Their presence would be suggestive but their absence not positively indicative.

3. When the adrenals are secondarily involved there may be bronzing of the skin. Cachexia is more early and pronounced than in cancer of any of the other viscera. Such symptoms as ascites may indicate general peritoneal carcinoma. Chylous ascites has been noted.

4. The tumor. This can usually be detected after a time, the date depending somewhat on the thickness of the abdominal wall. It often resembles a pyloric tumor, but is deeper and more fixed, often conveying a transmitted pulsation from the aorta. A double tumor has been noted more than once, the second being the distended gall bladder.

All observers agree that when pain, jaundice and tumor are present, the disease runs a rapidly active course. When jaundice is absent diagnosis is more difficult. It will be more easy when the characteristic faecal changes above mentioned are recognized. It will never, however, be really easy, and may be so difficult that primary cancer of the pancreas can only be surmised, not proved.

The disease rarely runs a course of over a few months and may terminate within ten weeks. Death may result from marasmus, from hemorrhage or from obstruction.

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Treatment—Medicinal treatment must be purely symptomatic, and I shall not consider it here. Surgical treatment, because of the obvious difficulties, can rarely be applied. Billroth twice partially resected some part of the pancreas, removing once a portion of the head with a cancerous pylorus and once the tail with a sarcomatous spleen.

Ruggi of Bologna is to be credited with the first successful operation on a primary cancer of the pancreas in 1890; the tumor was considered to be a retro-peritoneal adenosarcoma of either the kidney or pancreas. He operated from the loin by an oblique incision and exposed a soft, diffuse tumor (later proved to be carcinoma), with adherent small intestine and omentum. These were detached and the tumor, which weighed 23 ounces, removed. Complete recovery ensued. Gade's was the second successful case in 1895. He extirpated a tumor the size of a child's head from the tail of the pancreas. There were no metastases. Terrier in 1892 removed a five and one-half pound tumor as large as a man's head, but lost his patient. Robson tabulates altogether 13 cases of removal of solid tumors of the pancreas and adds a fourteenth of Malcolm's. To these there should be added Briggs' successful case of sarcoma. Of these 16, 8 recovered from the operation while the other 8 died within a few hours or days afterward. Thus, after all, the outlook for radical surgery in solid tumors of the pancreas is not wholly unpromising.

Unfortunately it is but rarely we shall have to deal with cases of this kind. The prejudices of the internists against early surgical procedures, and the fear of operation which deters so many patients, will long combine to keep these cases out of the surgeon's hands until too late for radical measures and until a time when only palliative procedures are possible. Among these, cholecystenterostomy is the only one which appeals to a trained surgical instinct and then only in selected cases. A study of the few reported instances, some ten in number, shows that though there was temporary improvement in most of them, as in seventeen cases of cholecystotomy, still, death was not long postponed, although much comfort was reported. Cholecystotomy has so little to commend it as compared with cholecystenterostomy that it should be abandoned save in exceptional instances.

I have grouped all the malignant tumors of the pancreas under the general head of cancer. There is the same unfortunate confusion of terms here as in other respects, owing to international

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differences of meaning. For example, one author describes a giant-celled carcinoma, another a cystic epithelioma, yet others, adenocarcinoma and adenosarcoma. It is most difficult to reduce all of these to a systematic nomenclature, but viewed from a clinical standpoint we may regard these histological differences as of minor importance.

ADENOMA—Nicholls, of Montreal (*Jour. of Med. Research,* November, 1902, page 385), has recently carefully gone over the literature of adenoma of the pancreas, of which he describes a typical case met with post mortem. He has been able to find but four other recorded cases which would stand the test, though one of these was doubtful, while several cases described as adenoma were in all probability malignant. There is of course a likelihood that certain cysts spoken of as cyst-adenoma had their beginnings in real adenomata, but the subject is and must long remain much confused. There is no probability that any such growth can be accurately recognized without exploration. Should it be met with during an operation the effort may be legitimately made to enucleate or extirpate it.

TUBERCULOSIS — Tuberculosis of the pancreas is generally regarded as exceedingly rare. Kudrewetzky, in 1892, however, challenged this statement. He found 44 per cent. of tubercular children showing pancreatic tuberculosis and 9 per cent. of adults. In eighteen cases of miliary tuberculosis he found it in six; nevertheless, as a primary lesion it is certainly rare. Cases reported by Mayo and Sendler illustrate how tumors in the region of the pancreas may be due to tubercular disease. Sendler, for example, opened the abdomen of a thin woman who had a movable tumor above the umbilicus. He found behind the stomach a hard tumor the size of a walnut, which he extirpated. This proved to be a tuberculous lymph node of the pancreas. The patient recovered. (This case is included among those referred to above of removal of solid tumors of the pancreas.) (La Tuberculose du Pancréas. *Thése de Paris,* 1899.) Lohéac has shown that pancreatic tuberculosis may assume either the form of gummatous nodules or of diffuse interstitial proliferation. He would explain the relative infrequency of tubercular disease in this location by virtue of the peculiar pancreatic secretion which he thinks to be protective as against this kind of infection.

SYPHILIS—Like tuberculosis, syphilis produces in the pancreas lesions of two kinds, the indurative and the gummatous, which can co-exist, the former being much more frequent. The latter has been observed in a six-months foetus. It does not appear that these

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lesions have ever been diagnosed intra vitam. Doubtless they occur with many cases of visceral syphilis, which, being recognized, are subjected to suitable and prolonged treatment. There is no known reason why a gumma of the pancreas should not respond to such treatment as readily as does gumma of the liver. As yet these cases have escaped the recognition and the attack of the surgeon.

PANCREATIC LITHIASIS — Kinnicutt (*Am. Jour. of the Med. Sciences,* December, 1902, p. 948) has been able to collect but seven cases, including one of his own, in which a diagnosis of pancreatic lithiasis was made. In Caparelli's case over one hundred small calculi were discharged through a pancreatic abscess and fistula which finally closed, closure being followed by diabetes. Three of the six died, and in one of them the pancreas was found riddled with abscesses. In Kinnicutt's own case biliary and pancreatic calculi co-existed. He suggests that just as the former result from infection of the biliary passages, so do the latter from an infection traveling up the pancreatic duct.

In the absence of pancreatic calculi in the stools there are absolutely no diagnostic symptoms. Subjective symptoms are common to too many lesions of various organs. Pain along the left costal arch is suggestive, but not pathognomonic; neither is the occurrence of undigested muscle-fibre in the stools, since this may occur in diarrhoea. Fatty stools are not often a frequent evidence of pancreatic disease, since in 330 cases collected by Ancelet (*Etudes sur les Mal. du Pancreas,* Paris, 1864), it was noted only 28 times. When present they may be due to co-existence of jaundice with greatly diminished absorption of fat. The most reliable evidence in this regard pertains to failure in the fat-splitting function. Normally at least three-quarters of the fat contained in the faeces should appear in the form of fatty acids and soap, even when jaundice is present, but when pancreatic juice is prevented from entering the intestine this decomposition is greatly interfered with. The presence or absence of jaundice is of small import so far as pancreatic lesions are concerned. Glycosuria is quite suggestive though met with usually only after the disease has well advanced. The discovery of pancreatic calculi in the stools being so rare, it will be seen that the evidences of pancreatic lithiasis are always very scanty; nevertheless, attacks of colic in the upper abdomen with or without jaundice, with undigested muscle fibres in the stools and evidences of diminished fat-splitting, and glycosuria, may properly lead to a tentative diagnosis of this condition, which may be confirmed if fragile concretions

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destitute of biliary pigment and cholesterin are found in the evacuations.

Conclusions—The writer is well aware that this is but a hurried survey of what most interests the surgeon and what he can accomplish by operation upon the pancreas. The result of most careful study and deliberation is to formulate advice in this brief sentence; that a well-founded suspicion of a palpable pancreatic lesion of acute or neoplastic character justifies an early exploration for its recognition and prospective relief, and that when a careful study of the case still leaves one in honest doubt regarding its nature, then the best rule to follow will be to operate.*

Discussion.

Dr. Charles G. Stockton:—I think I might best spend the short time allotted to me in expressing my charm in listening to the admirable papers that have been presented to us. However, I will refer to a few of the difficulties that still remain in spite of all we have heard. To begin with, I would like to draw attention to the fact that the question of diabetes does not seem to be settled from what we yet know concerning the pathology of the pancreas, and there still seems reason to believe that diabetes may exist without ascertainable disease of the pancreas. There is one interesting point of importance which is usually overlooked, and that is polyuria, as we have cases in which relatively a large amount of sugar appears without a corresponding increase in the amount of urine. On the other hand, there are cases in which there is a large amount of urine, and not much sugar. Polyuria must be considered, as it is in some way related to disease of the pancreas. An interesting case along this line was recently reported, in which the patient was operated upon for a cyst of the pancreas, and a short time after glycosuria appeared. A year later this was much worse, and in a few years there was distinct diabetes. Physiologists have found that the secretion of the stomach acts as a normal stimulus to the secretion of pancreatic juice, and that if the stomach secretion is diminished, the secretion of the pancreas should be diminished, as also intestinal digestion. Clinically, this is not the case. Where there is

* I have not attached hereto a bibliography. Those articles to which I have referred which are not included in Oser's bibliography, I have quoted in the text. To this I might perhaps add a reference to a paper of my own on the Surgery of the Pancreas published in the Medical News of February 15, 1902.

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a disappearance of the gastric juice in the interesting condition known as achylia gastrica, we find that the intestinal digestion is but little disturbed, or that it is normal.

In reference to inflammations of the pancreas, I would like to ask for a little delay before we accept the classification which has been suggested by Mr. Robson, and favored by Prof. Mikulicz and Prof. Park. Acute, subacute and chronic is not a good classification for pancreatitis, and before accepting this we should be more certain of the fact that inflammatory processes of the pancreas are like inflammatory processes of other parts. We have certainly had instances of inflammatory disease at the head of the pancreas which has been invaded by bacteria, but we have many instances of induration of the pancreas which we cannot attribute to infection. This induration is more of the nature of a cirrhosis of the liver, with which it is sometimes associated. As to the acute inflammations, are we quite justified in assuming that that form of acute inflammation which Prof. Fitz calls gangrenous, is merely the result of the presence of organisms finding their way through the ducts? It seems to me very unlike an ordinary gangrenous process. Another reason for delay in deciding is the necessity of more thoroughly understanding that singular phenomenon, hemorrhage from the pancreas, as this is the question still to be answered. The fact has been suggested by Mr. Robson that the hemorrhage may depend upon the presence of glycerine. This would not explain the numerous cases in which we find hemorrhage present before fat-necrosis takes place. Hemorrhagic pancreatitis may result from arterial disease, although it is claimed this has been disproven, but it does not seem to be satisfactory to say that it comes from diathesis. The hemorrhages are too frequent, too often dominate the whole process, and seem themselves to be the beginning of much of the subsequent pathological change.

Dr. Herbert U. Williams:—I feel that I cannot do better than follow the lines taken by Dr. Stockton in pointing out certain respects in which our information is still deficient. In some points our knowledge of pancreatitis and fat-necrosis is remarkable and as far as I can think at this moment it is unique in pathology. We are able, with tolerable certainty, to state that fat-necrosis is due to a ferment, and also to say that this ferment has a definite source. It seems to me that at abdominal operations fat-necrosis should always be borne in mind. The diagnosis of this condition is very easy and

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can be made in a few minutes with the aid of the microscope. It would furnish very valuable information. This fact, in my opinion, should be widely circulated. The presence of extensive fat-necrosis is almost certain to mean that there has been leakage of pancreatic juice.

I started out to consider some respects in which our knowledge is deficient. Dr. Flexner indicated that in the production of fat-necrosis there is possibly another factor at work besides the ferment which splits fat, and that this factor is in all probability derived from the pancreas. It is possibly in part trypsin. The existence of some factor besides the fat-splitting ferment is quite strongly indicated in the recent experiments of Wells. It was suggested long ago that the action of the pancreatic juices upon the blood-vessels might account for the hemorrhage which so frequently accompanies pancreatitis, and I would like to mention an experience I have had which may possibly elicit information in the same direction. I have recently had an opportunity of making Kaiserling preparations of two specimens of hemorrhagic pancreatitis, and the results were extremely poor. The colors did not materalize, and I have thought possibly the action of the pancreatic juices had something to do with this result. I agree with the causation of acute pancreatitis as outlined by Dr. Flexner, and also as indicated by Dr. Opie, referring in particular to the impaction of gallstones in the ampulla of Vater and the possible regurgitation of gastric juice. I would suggest the addition of traumatism to these, and also catarrh, extending from the duodenum or the bile ducts. These things are known to be quite competent to cause the phenomena of acute pancreatitis. Nevertheless it may be doubted whether they account for all cases. It has always seemed to me a rather mysterious combination that we find in this disease and that there is still some factor that we have not yet discovered. It may be that the unknown factor is the one which, as I have just said, seems to act with the fat-splitting ferment in producing fat-necrosis. I do not think sufficient attention has been paid to the work of Chiari on self-digestion of the pancreas, which is most important.

I have endeavored to indicate in a very rough way the general line of thought that it seems to me should be followed in our further work, and I hope I have been able to bring out this idea in the few moments I have had. One often finds areas of fat-necrosis at autopsies, and sometimes these areas are associated with areas of hemorrhage. I do not see any difference between mild cases of this

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character and fatal cases of multiple fat-necrosis and hemorrhagic pancreatitis, except one of degree. Although we are accustomed to meet only with the very severe and fatal grade at autopsy, the milder forms probably also occur quite frequently.

DR. MAURICE H. RICHARDSON:—The future of pancreatic surgery from the present indications seems less likely to be prolific of brilliant results than did the surgery of the biliary passages ten or fifteen years ago. We were led into investigating the acute lesions of the pancreas in many cases by the false diagnosis of appendicitis or some other acute lesion. We found in the beginning a frightful mortality. Patients died almost invariably whose symptoms, if caused by a gangrenous appendix, would in a large percentage of cases have recovered. After the accurate diagnoses of acute pancreatitis which Fitz was able to make soon after the publication of his classical monograph, immediate exploration was almost surely fatal. With increased experience in making an early diagnosis the same unfavorable results have followed, though not always so quickly, and in those apparently more favorable cases in which temporary improvement has followed drainage death has been none the less certain, although perhaps it has been delayed for weeks. At the Massachusetts General Hospital all the operative cases recorded as acute hemorrhagic pancreatitis, four in number, were fatal; a fifth case, one of acute pancreatitis, and a sixth, one of subacute pancreatitis, also died. On the other hand, those cases in which there was simply an abscess, under the influence of drainage proved favorable. My private experience has been similar, two patients improving rapidly after drainage, only to succumb to prolonged suppuration in which the pancreas became apparently totally necrotic. The disease in my experience has been but seldom diagnosed before operation, as you so often have no symptoms, subjective or objective, upon which to base a sound opinion. The lesion has been usually an unexpected one. In one or two cases the pressure of a tumor has led to a correct diagnosis. In my observation of these cases I have been impressed by the obscurity of the onset, the irregularity of the symptoms, and absence of localizing signs. The lesion has taken place in patients at or beyond middle life of unfavorable physique and of poor resistance: In one case, however, the pancreas was hemorrhagic in the beginning, and later totally gangrenous. The patient was a young girl of eighteen or twenty. I have been so deeply impressed by the unfavorable outlook in this

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lesion that I undertake operation with reluctance, especially in the stout, flabby, middle-age patients in whom it is most likely to occur. So rapid and fatal is the clinical progress of acute pancreatic disease, that but seldom can surgery oppose it, except as a forlorn hope. Acute infections comprising the whole gland permit only drainage, and that drainage, unless it be to the left flank, as well as through the epigastrium, is up-hill. Drainage does not check the progress of necrosis; sphacelation and removal of the sphacelus are requisite to recovery. The patient, therefore, who resists successfully a most formidable onset, must withstand a violent and exhausting suppuration in the heart of the abdomen, deprived of a most important, if not essential, organ of nutrition. But there are suppurations apparently dependent upon less extensive necroses, well localized abscesses of comparatively slow onset, and mild curve, which suppurations result in well localized and strongly confined abscesses, easily drained by a simple incision. Of these the hospital records show three, to which I can add a fourth, all favorable. In these cases the evidence was not absolutely conclusive, and the recovery of the patients precluded thorough demonstration. The patients survived the onset long enough to prevent the simple problem of drainage. I have found in several laparotomies, undertaken for various aseptic lesions, disseminated yellow areas which seemed possibly the remains of fat necrosis. These appearances were not attended by any palpable abnormalities of the pancreas itself. My observations upon cysts of the pancreas, benign new growths, though limited in all to six or less, has been invariably favorable. The surgery of these lesions is, I think, a brilliant field. The number of cases is necessarily small. I have found no palpable lesions of the pancreas in those digital explorations of the pancreatic area which I have of late years made as a systematic procedure. It is different in connection with the surgery of the biliary passages. The necessity for painstaking palpations of the common duct in the search for gallstones has revealed not a few enlargements of the head of the pancreas. In my first cases of this kind the detection of a hard mass involving the head of the pancreas and associated with jaundice led to the diagnosis of cancer, and in many cases this diagnosis was undoubtedly correct. When, after cholecystotomy, instead of dying, the patient recovered, I was convinced of the possibilities of error. When recovery became the rule, and death the exception, it seemed clear that drainage of the biliary passages had something to do with recovery, and hence the connection between gall-

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stones and the so-called chronic pancreatitis. The patients with jaundice, gallstones, and an enlarged pancreas, who recover under drainage, through cholecystotomy, have in my experience all recovered, and thus far permanently. I, for one, do not feel satisfied with the explanation of this fact, though much gratified by it. Why deviation of the biliary stream through the abdominal wound should have any influence upon pancreatic drainage I do not understand. In the jaundice of pancreatic disease, the common duct is obstructed, and the bile cannot pass by that obstruction to the duodenum, neither can pancreatic fluids pass back through the gall bladder and abdominal wound. There is much left to be discovered in the relations between gallstones and pancreatic disease, gratifying as are the results of operations of the former in the relief of symptoms apparently owing to the latter. Much can be added to our knowledge of pancreatic disease by careful examinations during abdominal operations, especially when the abdominal incision permits inspection, as well as palpation. Unless much more is learned concerning acute infections of this important organ, and especially its earliest manifestations, the future of acute pancreatitis promises little improvement upon the present results of surgical treatment. It is in the treatment of aseptic conditions, whether cysts, neoplasms, stones, chronic enlargements, wounds and injuries that surgery has a successful, brilliant and encouraging, though limited field. Even in traumatic conditions, however, through the baneful local influence of the pancreatic secretions, the outlook for successful treatment is always grave. On the whole, therefore, the surgery of the pancreas is encouraging, even in the most aggressive lesions. This field of surgery cannot rival that of the gall bladder or of the appendix in the wide applicability of surgical measures, or in the almost invariable success of them. It is a field, however, which encourages abundant research, the results of which, let us hope, will add a new chapter to the brilliant achievements of medicine and surgery.

Mr. B. S. A. Moynihan, of Leeds, England:—I am extremely glad to have the opportunity of joining in this discussion if it is only to bear testimony to the excellent work that is being done on this side of the Atlantic. I would like to add my personal testimony to the extremely good work Dr. Opie has done. We consider that the light he has thrown on this work is most brilliant.

I will consider for a moment the relations of this disease to the gall bladder system, and to mention the fact that many cases of pancreatic

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disease are discovered when operating for gall bladder disease. The great majority of our cases of chronic pancreatitis have been discovered simply because we have gone a step further in our gall bladder operations. I have personally operated on fifteen cases of chronic pancreatitis, and all have recovered, two of them being especially interesting. In one of them the operation was done a year ago, the diagnosis having been made of "floating stone" and a history having been given of gall stones, but none was present in the ducts. There was very marked chronic pancreatitis affecting more than one-half of the gland. There were also many other symptoms, especially marked polyuria, the patient passing from eighty to ninety ounces daily. No sugar was present in the early part of the disease, but developed later. I drained the gall bladder for some time, but did not do a cholecystenterostomy. Satisfactory progress has been made and pain has been relieved, but five months ago glycosuria developed and the patient is dying from diabetes. The second case was diagnosed as chronic pancreatitis, and a calculus was found in the pancreatic duct, the diagnosis having been made with some certainty beforehand. On opening the abdomen I removed the stone, which was found to be composed of carbonate of lime. This is the first occasion on which a pancreatic stone was diagnosed and found by operation. Mr. Robson recently had the same experience. As to acute pancreatitis we have had a comparatively small experience. I have talked it over with several, but could not find more than seven or eight cases. I have had two, but I do not seem to be able to collect more than seven or eight. Both of my cases were associated with cholelithiasis, one recovering without operation, and the other died. Large cysts were found, and the contents, which I had examined, were found to be sterile. I wish again to bear testimony to the excellent work that is being done on this side of the Atlantic, as it has thrown considerable light upon the subject.

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THE MEDICAL AND SURGICAL ASPECTS OF THE DISEASES OF THE GALL BLADDER AND BILE DUCTS.

THE DISEASES OF THE GALL BLADDER AND THE BILE DUCTS, WITH ESPECIAL REFERENCE TO DISEASES OF THE STOMACH AND INTESTINES.

BY C. A. EWALD, M.D.

Professor of Internal Medicine at the Berlin University.

GENTLEMEN:—In acceding to the honourable request transmitted to me by the Executive Committee of the Congress of American Physicians and Surgeons, to take part in the discussion of the diseases of the gall bladder and bile ducts, I am conscious of the extreme difficulty of my task in speaking before this assembly of distinguished physicians; to do justice to you and my subject!

It is not my object to present to you a review of typical gall bladder diseases, inflammation of the gall bladder, the ducts, the contiguous parts or the many complications with their confusing symptoms; I will, however, give to you the cardinal points with regard to diagnosis and therapy, the results of my own experience.

It is a recognized fact, that our ideas concerning this disease have met with fundamental changes during the last ten to fifteen years. We now know that this condition is due to a bacterial infection and not to the presence of gallstones, the origin of which has always been more or less hypothetical.[1]

In accordance with the virulence of the bacteria the symptoms become mild or severe, acute or chronic. The necessary factors for the presence of such an infection are an invasion of bacteria either from the intestinal tract or from the blood and a stagnation of the bile.[2] Fresh bile is sterile. In the normal condition the ducts in the liver are free from bacteria, but in the lower portion of the common bile duct the bacilli coli communis, which, however, were perfectly harmless, have been found by some authors. Whenever a stagnation of the bile occurs at any point of the system, there is always a favorable opportunity afforded for a bacterial invasion followed by various pathological changes in the gall bladder and ducts.

More frequently the bacteria appear from the intestinal tract, less so from the blood. The latter origin is the more uncertain as the

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lesion begins in the gall bladder, and remains confined to it and the contiguous parts, in nearly all cases. After injecting bacteria into the blood of animals followed by the non-appearance of these bacteria in the gall bladder, Sherrington concluded that the bacterial infection never originated from the blood. On the contrary, however, Welch found, three to four months after he had injected typhoid bacteria into the blood of rabbits, the bacteria to be present in the gall bladder but absent from every other organ. We would suppose whenever a bacteraemia is present, that there would follow at first a cholangitis and then a cholecystitis. But this is not the case. The process begins always in the gall bladder, as it is rather a diverticulum of the ducts and thereby affords the best opportunity for the stagnation of the bile. Perhaps there are also such influences as adhesions resulting from former circumscribed peritonitis, or the tight lacing indulged in by the female sex.

There is little need for me to remind you of the various microorganisms found to be the invading germs. Most frequently the bacterium coli is found. In a series of 128 cases operated in Professor Czerny's klinik at Heidelberg and collected by Merk,[3] there was in 53 per cent. the bacterium coli alone or with strepto- and staphylococci and in 30 per cent. the bile was found sterile. From the latter we must not conclude that bacteria were never present, for they may have died off as occasionally shown by their presence in the gallstones and their absence from the bile. Those bacteria not from the coli group may have reached the gall bladder and ducts from the blood. Chiari[4] out of 22 cases of typhoid fever found the typhoid bacillus present in the gall bladder in 19 cases, 15 times alone and 4 times in company with other bacteria. Sailer[1] in 6 cases found the typhoid bacillus in pure culture in 3 cases. Chiari in 13 cases of typhoid fever found the wall of the gall bladder and ducts to be in an inflammatory condition.

But this bacterial infection is not confined to the inflammation of the wall of the gall bladder with its consequences. It may also be followed by the formation of gallstones. I do not wish to burden you with a statement of the process of their formation. We all agree now that stones arise from a catarrhal condition of the mucosa. The desquamation of the epithelium always acts as the first stage. We know that stones vary in size and number. We do not know, however, why stones appear in one patient and not in the other, the conditions in both being similarly conducive. We all have the bacterium coli in our intestinal tracts, still we have not all

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got gallstones. (But there may be some of you here with a latent stone in your bladder!) In every case of typhoid fever the typhoid bacillus does not always serve as a nucleus for the stone and when found in the latter the bacilli may have migrated into it, but not produced it. Chauffard found in 68 cases of cholecystitis only 18 who had previously had typhoid. In 66 cases of other diseases only 15 had had typhoid.

More seldom have stones been found in the smaller hepatic ducts, either alone or in company with stones in the gall bladder. It is questionable whether there is in such cases always a catarrhal condition followed by infection. William Hunter[24] in his investigations of the poisonous effects of tolnylendiamin which caused a catarrh of the smaller hepatic ducts concluded that chemical irritation could produce such a condition. "The liver," he says, "is constantly being called on to deal with products more or less harmful carried to it in the portal blood from the intestines. If these products possess any irritant qualities, this continuous excretion will tend to set up and maintain a certain degree of intrahepatic catarrh in direct proportion to any irritant qualities they possess. And this is precisely the state of things favoured in the chronic dyspeptic, in those who lead a sedentary life, in the 'bilious subject' generally."

This view of Hunter might hold true not only for the ducts but also for the gall bladder, but surely not in the majority or even in a small number of cases. Indeed we do know of one toxic substance which produces a chronic irritation of the liver and this is alcohol, but the occurrence of cirrhosis together with gallstones is so very infrequent that we cannot in consequence assume a chemical substance to be the causative factor of both conditions.

The reason for the stagnation of bile and the subsequent bacterial invasion is not definitely known and perhaps we must always consider predisposition. It is a fact that gallstones have occurred in many members of the same family. Dufour[5] in 338 cases found in 35 such to be the case. This also points to a predisposition.

A second important question is, when do stones, either in the bladder or in the surrounding parts, cause pain?

Up to the present time it has been believed that the pain began with the passage of the stone into the cystic duct and was brought about by the reflex contractions of the gall bladder and the ducts forcing the stone forwards. But why does the stone from the gall bladder attempt to leave through the cystic duct, often against the law of gravity? The reason for this is unknown. We do know,

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however, that the gall bladder at times becomes enlarged, either because of increased fluid or of obstruction of the ducts by a catarrhal swelling of the mucosa or both; this state of affairs causes pain. Riedel[6] and others have seen such cases in which at the time of operation the gall bladder did not show the presence of stones or of adhesions, but simply a cholecystitis. Nevertheless such cases had had severe and repeated colics. The increased fluid in the gall bladder increases the pressure within it and on account of the *vis a tergo* any stone lying before the entrance of the cystic duct is pushed forward.

We may have colic due to contraction from the presence of stone or colic due to inflammation. Some observers believe that most of the attacks are due to inflammation around the stone or even without the presence of stone, and are caused by the stretching of the inflamed parts. My own opinion is that colic is always caused by contractions. An inflammatory swelling, no matter how severe, can cause a continuous pain, but never a colic with its sudden onset and disappearance, and its acute character. The bladder and the pelvis of the kidneys may be distended with fluid and the urinary tract may be inflamed, the pain from which however will be dull in character, but never colicky. Against the view that the colic is due to inflammation stands the fact, that whenever a stone is passed the symptoms subside suddenly whilst the inflammation remains unchanged. In those cases observed by Riedel, Kehr,[7] Krukenberg[8] and others, perhaps there was a kink in the neck of the gall bladder, which by the manipulations became corrected at the time of the operation. Or the attacks were not those of true colic but due to a liver neurosis. To bring about a colic there must be some obstruction of the ducts, but I will not dispute, that an inflammation may indirectly produce such an obstruction. On the contrary there are a large number of cases, which after severe exertion or trauma have shown such immediate attacks of colicky pain that there was not sufficient time for the development of inflammation. These colics, therefore, can only be caused by a mobile stone.

For the diagnosis of gallstones there have always been three symptoms, namely: colic, icterus and tumor.

How often does colic occur with cholecystitis and how often with gallstone?

We internists, unfortunately, cannot give any reliable statistics as to the frequency of the symptoms, but must rely on those of the surgeons because many of our cases do not come to operation and

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the diagnosis, therefore, remains unconfirmed. Merck in Czerny's klinik found that colic occurred in 56 per cent. According to my experience this estimate is far too small, for in the last ten years I have seen but two cases without colic.

In most of the cases the pain is referred to the stomach region and not to the region of the gall bladder. Merck found this in 39 cases, i. e., in 55 per cent. In other cases the pain is present all over the abdomen. The length, frequency and the severity of the attacks are very irregular. When there is neither jaundice nor a tumor present, it is very difficult to differentiate from a liver neurosis and from diseases of the stomach, colon, pancreas or kidney.

Formerly some forms of colicky pains in the region of the liver were supposed to be neurotic and were described as such by Frerichs, Stokes and others. Their symptoms were not different from those of true colic. To differentiate: the attacks occur at the time of menstruation, are periodical and accompany other neurasthenic and hysteric manifestations. They may be caused by irritants, such as alcohol and tobacco. Swelling of the liver, gall bladder and spleen are not present, local inflammatory conditions do not occur and icterus is also absent. Carlsbad is injurious, as specific therapy has no result. Improvement and cure are brought about by treatment of the general condition of the patient.

The different kidney diseases attended by attacks of colic are easily recognized through a careful examination of the urine.

It is more difficult to differentiate appendicitis, especially when the appendix occupies an abnormal position, directed upwards and with its tip lying against the liver. Under such circumstances inflation of the colon is often of great assistance causing the appendix, if adhesions have not already been formed, with the painful point to change its location. A hyperleucocythosis speaks for a suppurative appendicitis and against gall bladder disease. Empyema of the gall bladder has no hyperleucocythosis.

Still more difficult to differentiate are those cases which I described as appendicitis larvata[9] and here inflation of the colon is also of great aid in the diagnosis.

In not a small number of cases pain may originate from the transverse colon because of a catarrhal, tuberculous or dysenteric colitis. With increasing peristalsis attacks of pain occur simulating those from the gall bladder. A careful examination of the stools, appearance of severe pain after filling the colon with water or air, the general examination of the patient, especially of the lungs, and the history, all help to differentiate.

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It is comparatively easy to recognize those pains accompanying a hernia of the linea alba. If you keep in mind that such conditions occur, you will not overlook them. Recently an American, Doctor Howard Lothrop[10] has given a good description of its occurrence. But of all those affections, those of the stomach and pancreas afford the greatest difficulty.

There are primary diseases of the stomach and pancreas which point rather to disease of the gall bladder, and, conversely, there are diseases of the gall bladder with secondary manifestations in the stomach and pancreas, that obscure the primary condition.

Under such circumstances the chemical examination of the stomach contents is very important. In gastric ulcer, erosion, and most cases of nervous gastralgia there is a permanent hyperacidity and hyperchlorhydria. In gall bladder colic chemical examination of the stomach contents during the interval shows no change. Nevertheless during the attack or immediately after it there may be an increase of hydrochloric acid in the stomach. The hyperchlorhydria disappears with the subsidence of the attack. This I have observed repeatedly, and I have also seen that a hyperchlorhydria can occur reflexly from the intestine, as for instance when caused by a tape-worm.

Nervous gastralgia involves the whole stomach and is not confined to the pyloric region. It is important, furthermore, to notice that pain in gastric ulcer occurs after the administration of food and occurs regularly, whereas gall bladder colic is irregular, appearing at varying intervals and frequently at night.

But the whole picture immediately becomes altered with the appearance of a cholecystitis, a pericholecystitis and the formation of adhesions between the gall bladder and stomach or with the duodenum. In this condition the pain occurs on account of a nervous irritation and is not easy to explain. Here only the history and other symptoms can be of assistance. One physician will diagnose a cholecystitis, another diagnoses a nervous disease, and has success with his therapy, whereas the course of the symptoms and the later operation show the presence of stone.

The diminished hydrochloric acid is another chemical factor which points to a severe stomach lesion.

Inflation of the stomach may be of assistance in cases of atony to decide whether this atony is primary or secondary.

The vomiting is of importance. Although the vomitus in pyloric insufficiency may be mixed with bile, large amounts of bile mixed

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with intestinal contents only will flow back into the stomach, when the gall bladder is blocked by a stone in the cysticus, and the bile, instead of collecting in the gall bladder, will flow continuously into the intestine. Under such circumstances, the discharge of bile into the intestine does not depend on contraction of the gall bladder during digestion, as in the normal state, but occurs as soon as the pressure of the bile in the biliary passages has overcome the resistance at the papilla of Vater. The bile flows in the empty stomach and causes most severe and exhausting vomiting.

As Glaser[11] has shown, there is doubtless a reflex nervous tract between the gall bladder and stomach. If the former contracts the latter will also contract and vice versa. It appears that the stomach is more sensitive than the gall bladder, since the pain and cramps are first located in the epigastrium and later in the gall bladder region. It also happens that the patient has spontaneous pain in the pit of the stomach, but this is free from tenderness while the gall bladder is painful to pressure.

Finally the microscopical examination of the stomach contents must not be omitted. Sarcina, yeast cells and long bacilli may be explained by a stomach lesion, either primary or secondary.

The so-called gastric crises of tabes may simulate gallstone colic, but the careful observer will avoid making a mistake by noting the nervous symptoms. One should therefore never forget to examine the nervous system in doubtful cases.

We must also differentiate between gall bladder colic and most cases of acute and chronic pancreatic disease.

Here the whole picture can be a symptom complex consisting of cramp-like pains in the upper right abdominal region, a painful tumor, jaundice (according to Fitz in one-fourth of the cases), irregular temperatures and dyspeptic symptoms—vomiting, diarrhoea, nausea, eructations and emaciation,—all of which does not differ from a cholelithiasis. Acute purulent or hæmorrhagic pancreatitis is the more readily mistaken for diseases of the gall bladder or passages as they frequently occur together or the latter may cause the former. Fuchs[12] mentions 23 cases in the literature where hæmorrhagic pancreatitis was combined with cholelithiasis and 22 cases where the pancreatitis was purulent and necrotic. Indeed very disagreeable surprises occur at operation and at autopsy. Oser in 1898 stated that these conditions were correctly diagnosed in but 5 cases. Riedel in 122 cases of gallstones found in 3 cases an induration of the head of the pancreas caused by a marked

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chronic interstitial inflammation, so that the hard tumor was looked upon as carcinoma.

In all these cases an alimentary glycosuria, the presence of sugar in the urine, fatty stools and pancreatic stones are of importance. The latter are easily recognized on account of their formation from calcium carbonate with traces of cholesterine without the presence of bilirubin calcium. Unfortunately such concrements are found in the stools of other diseases and diabetes or fatty stools does not necessarily point to pancreatic disease. Therefore the diagnosis always remains only a probable one.

Jaundice may be the result of a mechanical obstruction or of functional disturbance.

Mechanical obstruction may be either (1) from stones (2) from compression of the extrahepatic ducts through tumor, kinking or pressure from without and adhesions and (3) on account of inflammation of the walls of the ducts. This latter condition occurs in the absence of the other two when the stone is confined to the gall bladder or to the cysticus or when there is an infectious cholecystitis or cholangitis present without formation of a stone. The inflammation, however, always the result of infection, may also be present with stone in the hepatic or common bile ducts. Ehret and Stolz[13] believe that such an inflammation may produce jaundice notwithstanding the presence of a stone.

When the stone does not make a complete obstruction, as often happens, the mucosa may become inflamed and then block the channel. This swelling may subside and recur several times, which explains the change in the intensity of the jaundice. The stone may nevertheless remain in the duct, bile color the stools and bile pigment appear in the urine, and despite removal of the stone the cause of the jaundice is not removed. This also accounts for the enlarged gall bladder in some cases of cholelithiasis, whereas in other cases it remains unchanged and in still other cases the gall bladder may be atrophied. As the inflammation involves the smaller as well as the larger passages it may be localised to a smaller or larger portion of the liver and produce the corresponding symptoms. Most of the different forms of jaundice are clearly understood if we assume an infection of the biliary passages with or without the presence of stone.

An inflammation jaundice according to Riedel appears in 10 to 15 per cent. of the cases.

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As the inflammatory swelling of the ducts, however, is not sufficient in every case to occlude them, we must assume that jaundice also occurs from functional disturbances of the liver cells. The bile passes over into the blood instead of into the ducts, and this form of jaundice is called "Parapedesis of the bile," by Minkowski or "Diffusion icterus," by Liebermeister. It is clearly understood that such a cause of jaundice is only hypothetical.

In 16 cases without stone or tumor collected by Merck only one-fourth had jaundice. It is absent in 25 to 30 per cent. of all cases. Therefore jaundice is not a necessary attribute of gall bladder disease, although not long ago physicians hesitated in their diagnosis of gallstones when jaundice was absent.

A rapidly disappearing jaundice signifies a passage of the stone into the intestinal tract, whereas a compression jaundice remains unaltered.

In some cases after a colic bile pigment appears in the urine, although there is no jaundice. I have seen cases in which the bloodserum was already pigmented whilst any other evidence of biliary pigments in the skin or secretions was absolutely lacking.

Tumor of the gall bladder is more frequently absent than present. Merck found enlargement of the gall bladder in 11 per cent., Courvoisier[14] in 16 per cent. of cases, my own experience is about the same. A gall bladder may be easily palpated when there is a hydrops present, which may lead to considerable increase in size and often cause it to lie low in the abdomen. It may under such circumstances be mistaken for floating kidney, mesenteric growth, pancreatic cyst, etc., because there is apparently no connection between it and the lower border of the liver. Often there is an adhesion formed with the lower margin of the liver, dragging a tongue-shaped process downwards and forming the so-called Riedel lobe.

A gall bladder filled with bile never becomes as large as in a hydrops, purulent or otherwise.

Most frequently the bladder contracts around the stone, at first extends beyond the liver border and later atrophies. This conforms to Courvoisier's law that the tumor in carcinoma is always larger than in stone.

Tumors of the duodenum and pylorus are differentiated by their respiratory fixation and their change of position on inflation of the stomach with air. Floating kidneys can be pushed back into their normal position and on inflation from the colon the latter lies in front of the former. Pancreatic tumors lie deep in the abdomen

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and are not movable. Finally the history, jaundice, colic, character of the tumor are all to be considered, though all these symptoms do not make a positive diagnosis because, occasionally, carcinomatous nodules of the lower border of the liver or a lobular formation on account of a perihepatitis may simulate a gall bladder and operation only give the diagnosis. Aspiration of the gall bladder I consider a dangerous procedure and should only be done if the patient is prepared for operation. If the gall bladder does not contract immediately after such an aspiration, the contents may flow directly into the peritoneal cavity and cause infection. This aspiration is nothing more nor less than diagnostic inquisitiveness and gives no indication as to the necessity of an operation; the character of the tumor can be much better determined by an abdominal incision.

We finally have to consider the complications of a cholecystitis and a new growth. Here belong ulceration of the bladder wall with perforation and passage of stone into the adjacent organs or into the peritoneal cavity. Fortunately the latter occurs very rarely because adhesions with the surrounding parts hold the stone within their grasp. If the stone perforates into the peritoneal cavity, a fulminating peritonitis follows, the intensity of which is dependent on the virulence of the infecting bile. Some cases have been saved by immediate operation. Perforation may occur into the stomach and the stone may be vomited; they may also perforate into the small intestine, traverse the whole intestinal tract, and be passed from the rectum with little or very severe symptoms. In other cases stones may remain in the intestine and lead to obstruction; in such case the history is of importance because the perforation and passage of stone into the intestine are without any symptoms. I had two cases of ileus, in which I diagnosed obstruction due to gallstones because both patients years before had been to Carlsbad for cholelithiasis.

Not only stones, but also a purulent cholecystitis with enlargement of the gall bladder may lead to a paresis of the intestine and the movable gall bladder tumor can simulate an intussusception. This has been observed recently by both Lane[15] and Bogdanik.[16]

Finally, stones may perforate into the colon and cause a fistulous tract between the gall bladder, stomach and colon so that intestinal contents may be vomited.[17] In some cases a cicatricial stricture of the duodenum has occurred while the clinical course of the condition may lead to a diagnosis of carcinoma after ulcer of the pylorus. (Reach[18].)

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In other cases there may be stomach dilatation, the cause of which is uncertain, or there may be compression of the choledochus, duodenum, portal vein or inferior vena cava with thrombosis and their sequelae, such as ascites, oedema of the legs, stomach and intestinal hæmorrhages, etc. Infectious cholangitis is followed by multiple liver abscesses which may lead to subphrenic abscess and perforation through the diaphragm into the lung and bronchi.

Infection of the bile passages occurs less frequently with carcinoma than with stone. The chills, fever and septic symptoms of such an infection need no explanation; there is no necessity to mention all the complication that may follow.

Carcinoma of the gall bladder is complicated in 95 per cent. of the cases by cholelithiasis. This accounts for the fact that carcinoma is more frequent in women than in men. According to Ferrier and Amoray, the proportion is 4 to 1; according to Messer 75 to 23. I have seen but three cases in men.

As carcinoma of the gall bladder is primary in contradistinction to that of the liver the cause must naturally lie in the gall bladder itself and is undoubtedly brought about by the irritation of the stone. (Musser[19].) Why a stone occasionally causes only ulceration and not always carcinoma, we do not know. It must also be remembered that in carcinoma of the biliary passages gallstones were found, according to Devic and Gallavardin,[20] in 46 cases only 10 times. In the latter, 6 were in the gall bladder and without connection with the new growth, and in 3 cases the stones were above the growth. In women carcinoma of the biliary passages is less frequent than in men, 16 to 30, whereas the reverse holds true in cholelithiasis.

Such an investigation shows that stone in the gall bladder is but a problematic cause for carcinoma.

As long as carcinoma remains limited to the bladder or the cysticus, jaundice will only follow through complications such as compression, obstruction or pericholecystitis, kinking or adhesions. On this account a carcinoma may remain latent for a long time and may only show its presence by a carcinomatous intoxication, or by metastasis, or by obstruction of the choledochus and the surrounding parts, leading to glandular enlargement and ascitis and oedema. In addition there may be dyspeptic symptoms and metastatic formations in the liver, pylorus, pancreas, peritoneum, etc. An oligocythaemia with a relative hyperleucocytosis is present. A differential examination of the leucocytes was of no benefit to me.

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Carcinoma of the biliary passages per se, is only to considered when limited to the extra hepatic ducts. The choledochus becomes involved at the papilla of Vater, in carcinoma of the head of the pancreas, because of its anatomical relations in running along the posterior surface of the duodenum surrounded by the head of the pancreas and forming a connection with the duct of Wirsung. This passage may be so small that, as Opie[21] has found, a stone 3 mm in diameter may be unable to pass through. In 53 cases Devic and Gallavardin found carcinoma of the choledochus present 22 times, 16 times in the hepaticus, 15 times at the junction of the three ducts. The new growth is most frequently ring or button shaped. In such cases, blood or bile may occasionally be vomited; the liver and spleen are often enlarged—which helps to differentiate from carcinoma of the head of the pancreas. The latter, gallstones, cirrhosis of the liver, metastasis about the entrance of the vessels to the liver must all be differentiated, as any one of these conditions may lead to chronic jaundice and progressive cachexia.

It is easier to recognize those cases of stone causing obstruction because of the history, the repeated attacks of colic, the varying intensity of the jaundice, the occasional rise of temperature and the simultaneous presence of stone in the gall bladder. Much more difficult is the differentiation between a hypertrophic liver cirrhosis and carcinoma of the adjacent parts. The Laennec cirrhosis runs a course without jaundice, whereas the Hanot cirrhosis, which runs a course similar to carcinoma of the ducts, can only be recognized because of its slower progress. But in all cases, it is difficult to make a positive differential diagnosis and when this does occur it is due more to a fortunate coincidence than to a convincing diagnostic consideration. All in all we must confess that a positive diagnosis in diseases of the gall bladder may be sometimes as difficult or impossible, as it is easy to make in other cases. I have endeavored to give the different clinical points for such a diagnosis.

As to therapy, I wish to say a few words regarding the indications for operation, as I consider the internal treatment of cholelithiasis, etc., to be very uncertain. Although there are a large number of cases benefited by diatetic, hygienic, gymnastic and medical means, the latter including the waters of Carlsbad, Vichy, Neuenahr, etc., still we are never positive that benefit or a complete cure will result from such treatment. Radically, we ought to operate in every case to remove the cause, for the acute inflammation may subside, the stone may pass through the intestine and apparent cure follow, but

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we are never certain whether there may not be a recurrence, which may lead to fatal complications. We will therefore only treat cases internally in which there is no fear of bad results from such treatment.

Some surgeons consider the immediate operation to be the ideal therapy in every case of gall bladder disease. To my opinion the circumstances are similarly compared to those of appendicitis; as we cannot go to such extremes in every case of appendicitis, likewise we cannot in every case of gall bladder disease. And this much more so as the operations on the gall bladder, either for incision or for its removal, are much more difficult and much more severe in their consequences than operations for appendicitis.

All clinicians agree that favourable cases, that is where a stone has been passed and jaundice was present, should not be operated.

My own view is as follows: during the acute inflammatory stage and during colic, I use the known means for their relief, and in addition in such cases, I advise lavage of the stomach with hot water or the drinking of large quantities of hot water, or with a solution of nitras argenti (Ehrlich[25]); in a severe acute infection, immediate operation; cases with rapidly recurrent favourable attacks, we should treat rather internally, as the stones are probably of similar size and able to pass. After such attacks, the bile flows freely and the infection subsides.

In unfavourable cases with recurrent attacks, I advise operation, especially so when stones lie in the hepaticus or choledochus. If I can conclude that the stones remain either in the bladder or in the cysticus, I favor operation, but I allow latitude to a patient less disposed towards the surgeon, to continue his chances in the lottery of internal treatment.

In cases of long standing obstruction or compression jaundice I advise operation according to the individual; a positive diagnosis of compression jaundice, whatever its nature, indicates immediate operation. On the other hand, in cases of obstructive jaundice by stone, I believe such patients, if they can properly take care of themselves and use no extra exertion, can wait a much longer time than five weeks, as mentioned by some surgeons. (Körte[23].) I have seen such wait five or six months before operation. The same may hold true for the many complications brought about by a pericholecystitis. Theoretically it would be right to immediately operate and the dangers of the operation ought not to be considered. According to recent statistics by Kehr, the mortality rate is 4.0 per cent.

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An impartial observer, like myself, who has seen so many operations, knows that surgical interference even though it relieves the patient, may be followed in the course of the healing of the wound, by so many threatening circumstances, so much anxiety and the healing may be so slow, that we would prefer to spare him the operation if possible. The inconveniences of post-operative cicatrices are occasionally many; stones may be left behind or it may have been impossible to have removed all the stones, and finally we must not forget that parenchymatous hemorrhages in cases of long standing jaundice may be fatal. On this point I quite agree with the views expressed some years ago by my friend, R. H. Fitz[22], and quite recently by Harrington[27], who says: "Good surgery is the degree of benefit afforded to the patient by the operation, and not the ability to perform successfully the work undertaken."

Although a case may be favorable or may have been operated on, we should always use preventive means against recurrence. Riedel believes never to have seen true recurrences after operation, but that those so called were due to stones either overlooked or left behind. This may be so, but I do not see why after operation conditions in the ducts may not remain favorable to the formation of new stones; in fact, Grawitz and Hanseman have observed this to occur after operation. As we know that stagnation of bile predisposes to the formation of stones or to a cholangitis, we must make use of methods to prevent such. Dietetic and hygienic are preferable than medical means for this, but I will not forget to mention that lately W. Clemon[26] made use of "Eunatrol" (Oelsaures Natron), which gave me also good results in some cases.

Gentlemen, I fear that I have not given in this paper much that is new and interesting to you. I am assured, however, that your friendly reception is due not so much to my paper and to my person, but to my representation of German science. Unintentionally you will think of my famous teachers, Frerichs and Virchow, to whom many of you, either directly or indirectly, are no doubt thankful for some of your education.

Allow me to say that American science has been a very fertile soil for the seed taken from Germany; for a long time it has repaid with interest what it has derived from us, and furthermore, allow me to express the wish for a continued reciprocity.

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THE MEDICAL AND SURGICAL ASPECTS OF THE DISEASES OF THE GALL BLADDER AND BILE DUCTS.

DIAGNOSIS OF AFFECTIONS OF THE GALL BLADDER AND BILE DUCTS.

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INTRODUCTION.

It seems almost a work of supererogation to discuss the subject we are to consider to-day. In recent months so many and valuable have been the papers published that it has seemed the very words were taken out of the writer's mouth, so that what is to be said to-day smacks to him of repetition.

Comparison with Appendicitis. It need not, however, be vain repetition. The era we are about to enter upon bodes for good. It looks as if we would go through the cycles of activity and inactivity, as in the early periods of appendicitis, in the treatment of gall bladder infections.

Primary disease to be treated: We trust that this contribution will further the progress which the writer sincerely believes is the true one, to the end that primary disease of the gall bladder and gall ducts will be accurately diagnosed and precisely and hence thoroughly treated, so that secondary disease will be of relatively rare occurrence. Local causes, as displacements and conditions which give rise to external pressure, must be removed. As forced upon us now it is secondary manifestations we are up against, manifestations which imply complications so difficult to manage as to render the mortality one of alarming proportions.

Secondary disease fatal. The opprobrium of the medicine and surgery of gall duct and gall bladder affections arises because the death-rate in secondary affections is so high. Let us see to it that the primary ailments are cared for, blocking thereby the oncoming of secondary conditions.

Prognosis. If primary processes are recognized, in the future *cholelithiasis* with its enormous train of abnormal states, *obstructions* and *dilatations*, will be prevented. Modern treatment of these affections will result in success in the highest aim of our

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endeavor, prevention. Fifty years from now the many secondary phenomena will be as rare as those which are secondary to diseases now removed early, as cataract, appendicitis, vesical calculus and a host of other conditions. Students of that period will marvel at the reports of the cases of the present.

Morbid anatomy of future. It is interesting to picture what a blank there may be in the morbid anatomy of biliary affections fifty years hence. The present day pathologist should make haste to fit out his anatomical museum to full completion in respect to biliary pathology. We can point out that notwithstanding the extraordinary multiplicity of primary and secondary lesions, our museums contain but few illustrations of these processes.

Museum specimens few. A search of the museums of Philadelphia disclosed less than twenty prepared specimens, excluding gallstones, which a student could consult.

Surgeon's need. This was not surprising, for the writer has seen surgeon after surgeon operate on biliary disease when they had no conception of the anatomical complications that arise, as in a case of prolonged cholecystitis and cholelithiasis, and readily became involved, indeed lost, in a morbid anatomy quagmire, as effectually as if thrown into a yawning abyss in the dismal swamp. The first precept the writer would urge is,—surgeons should know morbid anatomy.

Terminal Infections. Before leaving the field of morbid anatomy a word further. The studies of the writer have impressed him with the great frequency the gall bladder and gall ducts have to do with the termination of life. In many, many cases, put down as senility, in cases of chronic disease as tuberculosis, cases of nephritis, of cardiac disease, death has not been due to these affections, but to terminal infections, the source of which was in the biliary apparatus. Terminal infections will therefore be prevented by the removal of primary foci.

General Summary.

1. *Morbid States.*

A. The primary morbid states of the gall bladder and gall ducts are:

Inflammations { catarrhal (rare).
infectious.

Morbid Growths (primary).

Parasite Invasions.

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B. The secondary morbid states are:

1. Causes outside of gall bladder and gall ducts.

   Inflammations { catarrhal { secondary to heart, lung, abdominal disease.
   infectious

   Morbid Growths.

   Obstructions { displacements and deformities.
   diseases outside the ducts.

2. Causes within gall bladder and gall ducts.

   Inflammations (including ulceration and perforation).

   Because of { displacements and deformities.
   morbid growths.

   Foreign Bodies { parasites.
   gallstones.

   Obstructions, because of
   Inflammations.
   Morbid Growths.
   Foreign Bodies.

   Enlargements, because of
   Inflammations.
   Morbid Growths.
   Foreign Bodies.
   Obstructions.

Unfortunately, the states which clinicians see are in the larger proportion of cases SECONDARY, and belong to

I. Local disease, as indicated above.
II. Diseases in remote parts.

PRIMARY MORBID STATES.

INFLAMMATION OF THE GALL DUCTS. CATARRHAL CHOLANGITIS. Causes, secondary to gastro-duodenal catarrh, to pressure, to local spreading infections. Other cases of catarrhal jaundice are found to be primarily infectious.

The *symptoms* and signs are well known. The age of the patient, the presence of a cause and the clinical course make up the picture. When long continued, catarrhal inflammation may resemble obstruction due to other primary or secondary processes.

The *diagnosis* in cases of so-called catarrhal jaundice, continuing more than six weeks, should be revised if the erythrocytes fall in number, the hæmogoblin drop, the spleen enlarges and there is loss of weight. The true nature can be determined by the ante-

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cedents or by accompaniments, which by this time may be more prominent, as the enlarged glands of syphilis or tuberculosis. Organic diseases, cirrhosis, cancer of the liver, infections, as Weil's disease, must be excluded. Many so-called catarrhs are the result of typhoid, pneumococcus or other infections.

Treatment. Medicinal. Hydro-therapy, including an abundance of water internally, enemata of cold water (Krull); compresses, baths. Proper diet (Carlsbad at home). Clothing. Exercise. Rest. Alkalies, iron, if anæmic. Ammonium chloride.

Surgical. Symptomatic operative interference compulsory, if obstruction complete, jaundice prolonged and patient toxic, liver enlarged, or spleen enlarged.

SUPPURATIVE CHOLANGITIS. Simulates pyelo-phlebitis, abscess of the liver, syphilis of the liver, rare cases of cancer, Weil's disease.

Diagnosis, based on 1. *Clinical course.* Onset gradual. Infection of ducts or gall bladder; foreign bodies as gallstones present, or a previous general infection.

2. *Objective diagnosis.* Icterus may or may not be present. Fever characteristic (hectic type). Toxic symptoms from sepsis of jaundice.

3. *Physical diagnosis.* Liver enlarged moderately. Tender. Tender area in region of the 12th dorsal vertebra from 2 to 3 cm. from the middle line (Boas).

4. *Laboratory diagnosis.* Leucocytosis. Serum reaction to determine cause. Blood examination to exclude malaria.

Differential diagnosis (see infections). Pyelo-phlebitis, absence of cause for infection in portal area. Amœbic abscess, clinical antecedents, physical diagnosis, absence of leucocytosis. Malaria, blood examinations. Simple cholelithiasis, no leucocytosis (see Ball-valve Calculus).

Treatment—Drainage. Patience and waiting of doubtful value.

CHOLECYSTITIS. Simulates hyperæmia and infections of the liver, sub-diaphragmatic abscess [see Mason's and Osler's papers], diaphragmatic pleurisy, pneumonia, pancreatic affections [see these transactions], perforations of ulcer of stomach or duodenum, intestinal obstructions, uræmia, endocarditis.

Diagnosis, based on 1. *Clinical course.* Primary follows acute gastroduodenitis, and general infections. Secondary follows infections induced by foreign bodies and obstruction. Any age, either

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sex; habits of but little consequence. Antecedents mentioned above. Onset vary; often fulminating, mild and gradual, severe (see case **, appendix).

2. *Subjective diagnosis.* Pain from spasm or tension, tenderness, nausea and vomiting.

3. *Objective diagnosis.* Fever, mild to severe. Remittent or intermittent. Chills in fulminating type. Jaundice not present.

4. *Physical diagnosis.* Tumor; end of 9th rib. Characteristics of swollen gall bladder. Movable with respiration unless inhibited by pain. Spasm of rectus.

5. *Laboratory diagnosis.* Leucocytosis in all infections except those due to typhoid fever. Present in 50 per cent. of latter. *Serum diagnosis.* Important, to determine nature of infection.

Cholecystitis in Typhoid Fever. The local infection may develop in the course of the disease,—during the third or fourth week; or in the period of convalescence. All grades are seen. It may or may not be accompanied by cholangitis. If it occurs in the course of the disease its onset may be marked by an increase in the temperature, varying with the intensity of the local infection. In mild forms the fever may become a little higher than the continued range that had preceded. In severe forms it may become remittent or intermittent and chills are not uncommon.

Nausea and vomiting are common in the beginning and may continue for several days. Pain in the region of the gall bladder, localized tenderness and rigidity of the right rectus muscle develop with the fever.

Fulminating cases may occur simulating perforation of the bowel, during the course of the disease.

The mode of onset and association with cholangitis is illustrated by case No. II. (see appendix). The symptoms are very characteristic. Pain is often so extreme as to simulate gallstones or lead to collapse. It is usually in the situation described, but may be referred to the epigastrium. The pain may seem to be general at first and even be marked away from the gall bladder, as in the right iliac fossæ. Often the pain is diffused during the first twenty-four hours and attended by general rigidity and distention. Frequently the local symptoms are overlooked and I am convinced many cases of so-called relapse in typhoid fever are due to mild cholecystitis.

Leucocytosis need not be present. The data is quite insufficient concerning this point. In one of my cases it was absent, although following the law of leucocyte increase, such absence might have been due to the extreme infection.

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Cholecystitis during the convalescence of typhoid fever is not unusual. Contrary to Da Costa's experience I have seen it quite as frequently at this period as any other. Here, too, the cases may be mild, fulminating and perforating. Case No. III. (see appendix) will illustrate the onset and course of a fulminating attack.

Briefly, the case No. III., seen with Dr. Rehfuss, was one of typhoid fever of long duration in a woman 56 years of age. Five days after the temperature was normal she was seized suddenly with severe diffused abdominal pain. The greatest tenderness seemed to be confined to the right iliac fossa. She had a chill coincidentally followed by fever and with both much prostration. I saw her two days after onset of pain. Although no defined tumor was present the pain, rigidity and tenderness were confined to right upper quadrant; vomiting persisted, tympany was marked. Three hours after my visit Dr. Edward Martin operated. In the interval the signs of inflammation extended over upper abdomen. The gall bladder was much enlarged and attached to neighboring organs by adhesions. It contained mucus and pus, both bile stained. No calculi, and ducts seemed free. Operation was followed by immediate relief and an uninterrupted convalescence. (See charts.)

Case No. IV. was one of onset more gradual after the typhoid process was completed. It is interesting to note that tenderness was absent, leucocytosis was absent, while chills and fever were dominant features. The chart herewith exhibited shows the course of the fever. The occurrence of *death* from *acute hemorrhagic pancreatitis* is most interesting in the light of recent researches.[1]

The onset in the post febrile period takes place in the first or second week, when we are about to place the patient on solid food. In consequence, the change of diet is held responsible for the pain, tympany and fever.

Confusion regarding secondary cholecystitis. Cholecystitis occuring in a subject who has gallstones or a displaced liver differs from primary cholecystitis in local rather than general symptoms. The altered position of the gall bladder changes the location of the pain and tumor. In a case operated on by Dr. Harte the tumor was below the transverse umbilical line, and in one operated on by Dr. Price the tumor was in the median line and the gall bladder had emptied its contents into the lesser peritoneal cavity. In the first, the tumor was continuous with liver dullness, in the second it was

[1] Since this paper was read Moynihan has reported a similar case in the Br. M. J. These are the first cases of this character reported.

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not. It is scarcely necessary to say the antecedent history of cholelithiasis aided in the diagnosis.

Differential diagnosis. My experiences of the past year lead me to believe cholecystitis can easily be recognized, the difficulty arising in distinguishing some forms of it from appendicitis being greatest, and yet these are cases of secondary cholecystitis and therefore more obscure because due to displaced gall bladders. Primary cholecystitis can be recognized by the clinical course, the physical signs and the associate symptoms, together with the results of laboratory diagnosis.

In the distinction between the *catarrhal* and *suppurative* varieties we are deciding in part between mild and severe forms of infection. The degree of the infection is estimated by the severity of the local symptoms and the intensity of the toxæmia as indicated by the fever, the cardio-vascular and cerebral symptoms and the leucocytosis. It is to be remembered that an intense alarming inflammation may arise without pus formation as in case No. I. (See appendix.) A clear fluid only was removed from the gall bladder.

1. *Congestion of the Liver.* In cases of acute infectious endocarditis with cardiac dilatation, the left lobe of the liver often enlarges and is the seat of pain and great tenderness. This is accompanied by jaundice. An enlarged gall bladder may be simulated, and as the general symptoms of infection prevail, that organ may be considered the site of primary infection. It is not unusual to have endocarditis without physical signs in the heart. Again, in a case of purulent pericarditis, the distention of the liver capsule was extreme, pain was excessive and the picture was not unlike that of suppuration of the biliary passages.

2. *Syphilis of the Liver.* The history may help, but who does not know how weak such help is in this infection. Antecedent and associate conditions aid us here. The fever is commonly intermittent in syphilis. The paroxysms are at fixed periods in the day, however. Leucocytosis is absent. Justin's sign is not satisfactory. A localized tumor with the characteristics of an enlarged gall bladder is usually not present. It may, however, exist, although it is not so tender. Case, a female, aged 32, who had been exposed to the possibility of infection was seized with pain, tenderness and swelling in the gall bladder region. She was told it was "cold" or "gallstones." Jaundice followed. The local tenderness and tumor continued but the jaundice disappeared. The mass simulated cancer of the pylorus. A moderate fever prevailed. Specific treatment dissipated the

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tumor, and all the symptoms vanished with it. There has been no recurrence in twelve years. A rapidly growing localized gumma attended by fever and sweats may simulate gall bladder infection. It has been the writer's experience to find a lymphocystosis more common in syphilis than in other infections.

3. *Multiple Abscess of the Liver or Pyelo-phlebitis. Portal Pyæmia.* The differential diagnosis is sometimes difficult or impossible. The antecedent history of abdominal infection is necessary to establish the diagnosis. The liver is large in multiple abscess; in cholecystitis, the gall bladder. Pain is not marked in multiple abscess. Ascites, enlarged, spleen, haematamesis and diarrhœa are more common in portal obstructions.

4. *Abscess of the Liver* occurring in amoebic dysentery is recognized by the history, by physical signs posteriorly rather than anteriorly, and often thoracic rather than abdominal, by the frequent absence of leucocytosis, the rarity of fever whose type is more or less slow and by the presence of uniform enlargement or enlargement in one direction of the liver. The spleen is more likely to be enlarged in abscess than in non-typhoid cholecystitis. Abscess of the liver is neither as painful nor as acute an infection, and, hence, not as intense an infection as cholecystitis.

5. *Secondary Cholecystitis.* It is to be remembered, we are considering only the differentiation of primary cholecystitis and hepatic affections. Secondary cholecystitis and cholangitis have the history of the primary cause.

6. *Sub-diaphragmatic Abscess.* History, physical signs, exploratory puncture avail (see papers of Mason, Osler and others). It manifests itself posteriorly and signs are abdominal as well as thoracic. Difficulty of diagnosis not great in primary cholecystitis.

7. *Diaphragmatic Pleurisy.* Diagnosis at times difficult. Exposure to cold feature in pleurisy. The following incidents in a case showed points in diagnosis. Patient robust, rheumatic. Operation for hemorrhoids. Three days after takes a cold bath. Symptoms of diaphragmatic pleurisy developed, suggestive of infection. Chill and fever. Leucocytosis absent. Rheumatism in other muscles.

8. *Pneumonia.* It is only necessary to call attention to the likelihood of confusing the infections in some cases. In pneumococcus infection with gastric and abdominal symptoms dominant, the pulse-respiration ratio and the expiratory grunt may alone suggest the lesion, especially in children. In those in whom jaundice occurs early the confusion may be increased.

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9. *Pancreatic Diseases.* They have been so exhaustively considered in the preceding papers of this Congress that it is not necessary to take them up on this occasion. (Pp. 1–104.)

10. *Perforations of Gastric and Duodenal Ulcer.* The diagnosis is sometimes difficult, but the marked difference in the previous history is most helpful. Without such carefully worked out history diagnosis may be impossible.

11. *Intestinal Obstruction.* This condition does not simulate hepatic and biliary disorders as frequently as it does pancreatic lesions. Time forbids an extensive review.

12. *Uraemia.* Like hysteria, uraemia can simulate almost any other condition. In that form in which abdominal pain and vomiting are most prominent, the surgeon may easily be led astray, particularly as albumin and casts are almost always present in gall bladder infections.

PRIMARY CANCER OF GALL BLADDER AND GALL DUCTS. The literature of this affection has been thoroughly studied. The collected cases by the writer, Courvoisier, Sugist, Ames, Kelynack, Rolleston and others are accessible. It may be said our knowledge of this condition is fairly definite.

PARASITES. Parasite invasions of the biliary passages as by hydatids or round worms lead to obstruction of the ducts and perhaps enlargement of the gall bladder, with secondary catarrhal or suppurative cholangitis. A shrewd guess at the diagnosis may be made by exclusion and by the antecedent history of these affections. Otherwise the cases fall under the head of inflammation or of obstruction of the biliary passages.

SECONDARY MORBID STATES.

It is not within the province of this paper to consider all the lesions that arise secondarily to primary morbid states. A few will be considered. Thus it is important to consider *Displacements* and *Deformities* of the liver, as they give rise to many pathological conditions of the ducts or simulate gall bladder diseases. It is hoped this study of gross conditions will lead to the study of less evident states, for the writer fully believes displacements are leading etiological factors in biliary affections and that we are ignorant of the relatively normal position of the liver and do not

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know when the liver is displaced in minor degrees. The prevention and treatment of minor displacements is obvious.

Morphology. In re gallstones and displacements it is rare to see cholelithiasis, not of infectious origin, in persons who are morphologically of normal type. The patient is too fat or too lean; too small in girth or perhaps too large; presents one of many abnormal types of thorax and abdomen.

1. DISPLACEMENTS AND DEFORMITIES.

Literature:—

1. Landau, Die Wanderleber, etc., 1885.
2. Faure, Paris Thesis, 1892.
3. Graham, Trans. Assoc. Amer. Phys., 1895, Vol. X, p. 258. Resumé 69 cases.
4. Packard, Univ. Med. Mag., 1897.
5. Teleky, Centralblatt fur die Grenezgebiete der Medicin and Chirurgie, 1901, p. 267.
6. Steele—Experimental Evidences of Biliary Obstruction in Floating Liver, Univ. Med. Mag., Dec., 1902.

DISPLACEMENTS. About 80 cases reported. Gall bladder and gall duct disease simulated because

1. Gallstone colic simulated by the obstruction of the ducts.
2. Obstructive jaundice due to kinking of ducts.
3. Tumor simulates gall bladder tumor.

Diagnosis. 1. General morphology suggestive. 2. Clinical course. Females—History trauma or abdominal disease-diastasis. Long duration. Recurrent attacks of pain, transient jaundice, bilious vomiting. Symptoms of pressure upon other organs. Neurasthenia—gastro-enteroptosis. Fever absent, except in a few cases.

3. *Physical Examination.*

1. Tumor size, shape, consistence and movability of liver.
2. Tympanitic note over normal area of liver dulness. *Note:*—Percuss in upright and recumbent posture. *Exception.*—Anteversion of liver when convex surface in contact with diaphragm and anterior abdominal walls—dullness not absent.
3. Palpation by Glenard's procédé du pouce.
4. Replaced by palpation or recumbent posture.

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DEFORMITIES. 1. *Floating Lobes.* Riedel's lobe. Tongue-like process. Gall bladder tumors simulated by elongated lobe.

Diagnosis. Clinical course uneventful; or tumor in which attacks of pain and tenderness. Usual occurrence in women, history of abdominal constriction. Attacks of gallstone colic and cholangitis, a coincidence or rarely a sequence.

Physical Examination. Tumor movable with respiration, variable size, tongue-like, connection with liver may or may not be demonstrated by percussion. Palpation; movable, sometimes disappears. In rare instances behaves like floating kidney. Percussion. Dull if thick; resonant if thin. Solid, smooth.

Cholecystitis simulated by tumor, which at times is the seat of pain and tenderness. *Cholelithiasis* a frequent accompaniment, the coincident giving rise to confusion.

2. *Corset Liver.* Gall bladder tumor simulated by this deformity.

Clinical course. Like that of floating lobe; associated with incidents of hepatic disease, hence may be coincident with choleystitis, cholangitis, cholelithiasis, gastro-enteroptosis and carcinoma.

Physical Examination. Tumor as in floating lobe. If separated from liver, variable size and shape, consistence of liver, movable to an extreme degree, never in loin, tender and swollen, always superficial, sometimes the seat of spontaneous pain.

LIMITATION OF OUR KNOWLEDGE IN BILIARY AFFECTIONS.

We have much to learn of the pathology and clinical course of these affections.

1. *Leucocytosis.* We cannot as yet consider it more than a symptom. The recorded cases are few that give information either by numerical or differential count. My observations go to show that leucocytosis is *present* in all *primary* infections except typhoid fever; absent or uncertain in all secondary infections. Its presence, therefore, points to a primary lesion.

2. *Hepatic function.* We have no clinical method of determining the degree or character of alteration of function in hepatic, much less biliary disorders. The studies of Edsall, incorporated later, show how little we can rely on the urine for the clinical diagnosis of hepatic disorders. Perhaps we need a research hospital for the study of hepatic disease more than of any other organs.

3. *Displacements* are obscure. We do not know what constitutes a displacement sufficient to predispose if not excite biliary disorder. The questions of morphology and preventive measures are too vast

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for discussion. It is not dislocations but minor displacements of which we must learn more. What degree of displacement gives rise to impeded circulation of the bile in the channels—interferes with bile drainage.

4. *Treatment.* We have now accurate knowledge of the effects of treatment. Do "cures" postpone the evil day? How many persons get well permanently and without secondary states always pending, if not in full blast. Is it worth while waiting for medicinal treatment in primary cases? How many get well in this manner and how many experience temporary cure,even if they get relief? Finally, do surgical measures in acute primary infections prevent secondary states? It seems too soon to answer the latter question. My personal experience supports the knife as the best cure in cholecystitis.

5. *Morbid Anatomy.* The young surgeon should see the autopsies of at least 500 cases of old people whereby at least 100 cases of secondary diseases of the gall bladder and gall ducts would be studied.

6. *Operative Measures.* When should an operation be advised? 1. *Primary states. Catarrhal cholangitis,* if chronic, i. e. six weeks to two months; no improvement; blood falling; if the time required for blood-clotting increases; spleen and liver enlarging. *Suppuration;* in all cases, if no relief to any one symptom in three days; if liver does not increase, if fever falls, if leucocytes fall, if jaundice improves, expectant treatment. *Cholecystitis;* operation perhaps should be performed in every case. Certainly operate in fulminating cases with sepsis and progressive toxaemia; leucocytes, increasing or stationary. If cultures or serum reaction indicates the infective organism, be guided by its character. A colon infection means operation. The question of operative interference must be decided not alone by laboratory investigation but by clinical sense. If a patient is sick to-day, sicker the next day and is a little more toxic and septic each day, an operation should be done in spite of the absence of leucocytosis. The matter is one of degree of illness and in each case the clinical acumen of the physician must stand in some service.

Nephritis is not a contra-indication against operation. "Bile" and septic nephritis is quickly relieved by the operation.

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Definite Knowledge Concerning Biliary Affections.

We deem it can be said that we have fairly definite knowledge concerning diseases of the gall bladder and gall ducts. With the limitations already described borne in mind we can say we have a good picture of

1. Acute catarrhal and suppurative cholangitis.
2. Cholecystitis.
3. Primary carcinoma.
4. Displaced or deformed liver if in excess.
5. Ball-valve calculus, a symptom group well worked out by Naunyn, Fenger, Osler and others.
6. Courvoisier's Law.
7. Points in physical diagnosis described under special diagnosis.
8. Points in laboratory diagnosis.

Special Diagnosis.

We must determine if there is present,

A. As primary states,
- Inflammation.
- Morbid Growth.
- Parasitic Invasion.

B. As secondary states,
- Inflammation and its results.
- Cholelithiasis.
- Obstruction { displacements and deformity. / inflammation. / foreign bodies. / external disease. }
- Morbid Growth.
- Enlargements.

The recognition of primary or secondary states can only be obtained by the employment of all means of diagnosis at our command.

It may be said *laboratory* and *physical diagnosis* are of the greater value in *primary* states of the biliary passages; *historical* diagnosis in the *secondary* states. Some points elicited by each method are herein detailed.

Subjective Diagnosis. The various subjective symptoms and their vagaries are familiar. It is well to recall that the pain of gall bladder disease is due to inflammation, to distention, to colic or

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spasm induced by a foreign body (gallstones). The pain due to inflammation and spasm must be distinguished from:

1. Dietl's crises, in floating kidneys, which may be accompanied by jaundice.

2. Crises occurring in dilated and displaced stomachs, first described by Kussmaul, due to kinking and stenosis of first and second portions of duodenum, especially if adhesions have taken place.

3. Crises due to downward displacement of liver (36% of cases—Steele).

4. Renal calculi.

5. Pancreatic pain.
   Hemorrhagic pancreatitis.
   Acute pancreatitis, occasional jaundice.
   Pancreatic colic, crisis and sometimes jaundice.

6. Gastric ulcer with local peritonitis.

7. Duodenal ulcer—jaundice in a small proportion of cases.

8. Gastric neuroses.

9. Abdominal pain of thoracic disease, as pneumonia, diaphragmatic pleurisy.

10. Disease of the vertebra—tuberculous and rhyzomilic.

11. Appendicitis.

12. Intestinal pain.
   Acute ileo-colitis.
   Lead colic.
   Epigastric hernia.

13. Gastric crises of locomotor ataxia.

14. Peritoneal pains of toxic origin often occurring in uraemia—pain in upper half of abdomen, more or less collapse with nausea and vomiting.

15. Pain resulting from a forgotten fracture of rib with callus pinching the nerve.

16. Aneurism of aorta.

17. Obscure alleged neuralgias of the liver.

Objective Diagnosis. Nothing unusual need be pointed out except as to the temperature.

Fever. We have striking temperature ranges in hepatic disorder. One type to which Charcot first called attention is intermitting. This type, usually associated with ball-valve calculus, may be confounded with malaria (plasmodium), septicaemia (blood cultures, strepto- and gonococcus, or examinations of pus). Endocarditis (same means of diagnosis), with recurring fever (Ebstein's disease)

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due to lymphatic tuberculosis (tuberculin test.) It is this type of fever that is seen in syphilis, and such a cause must be excluded. Murphy calls attention to the rapid rise and fall of the temperature in such cases.

Physical Diagnosis. The following methods secure valuable facts, and must be employed in each case:

1. Inspection—Fixation or restriction of side.

2. Palpation—To find out if pain, tenderness swelling or spasm are present.

(1) Simple. *a.* Tenderness at Mayo Robson's point, at juncture of outer one-third with inner two-third of line drawn from tip of ninth right cartilage to umbilicus. *b.* Outline tumor. If inflamed gall bladder, continuous with liver; if distended movable, pear shaped, neck towards liver having a tendency to disappear and bob up again.

(2) Bi-manual. Fluctuation—Gallstone rubbing.

(3) Method of Glenard.

(4) Eight fingers. Pressure upon four placed over part by four of other hand, the fingers of hand not pressing relaxed. (Pottalschek.)

(5) Hooking fingers under rib in region of gall bladder or pressing deeply in this region while patient takes full breath. (Murphy.)

(6) Deep prod with closed fist (Jordan-Lloyd) over gall bladder, excites pain if gallstones.

3. Percussion—Outline tumor, note if continuous with liver (a), an interval of resonance may exist between the liver and gall bladder tumors. Ausculatory percussion not conclusive. Note, however, percussion must be employed in both upright and recumbent posture to detect displacements of liver.

4. Auscultation — Friction of perihepatitis; gallstone crepitus (rare).

X-Rays. Of some value in the hands of Beck. Usually considered doubtful.

Exploratory puncture. Not justifiable.

Laboratory Diagnosis. The Blood. Leucocytosis. It is remarkable how few reports are made. Fuller information is required on this important point. It is present in acute cholecystitis and cholangitis not typhoid. Its presence points to streptococcus infections, to pneumococcus infections, to bacillus coli infections, and excludes typhoid, malarial and tuberculous infections. It often excludes amoebic abscess, but does not exclude multiple abscess of the liver. If lymphocytes are in excess syphilis is suggested.

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Iodophilia. Locke and Cabot found positive reaction in five cases of gall ducts out of seven. Their studies, however, showed positive results in a very large percentage of cases in which suppuration prevailed. One can place about the same value upon it as upon leucocytosis.

Red Blood Count. This should be made repeatedly. In jaundice it falls rapidly and the degree of reduction should guide one in the indications for operation.

Coagulation Time. A close watch of the blood should be made with Wright's tubes. The normal coagulation time is two to four minutes. In jaundice the blood may coagulate so slowly that eight to ten minutes may elapse before clotting is completed.

Tuberculin Test. Jaundice may be due to enlarged lymphatic glands pressing on the ducts. Recurrent fever (Ebstein's) attends it. It may simulate gall bladder infections. A tumor of the liver so situated as to resemble an enlarged gall bladder may be tuberculous. The test mentioned will give the characteristic reaction.

The Urine. (From studies by Dr. Edsall.) The presence of bilirubin indicates obstruction. Observers have long tried to find some indications from urinary analyses to distinguish the various forms of hepatic disease and differentiate between liver and gall duct disease. My colleague, Dr. Edsall, has been engaged in these studies and has studied some of my cases, and I am permitted to give his results.

The results are, like those of others that have done similar work, either negative or extremely inconclusive. They may have some interest. His report is as follows:

"(1) The neutral sulphur of the urine was early determined to be increased in certain disorders of the liver. I estimated the neutral sulphur in a series of cases of liver disease with and without jaundice, in connection with some other urinary constituents. The results were very irregular and seemed to be of absolutely no consequence in diagnosis, as was to have been expected from the general physiological standpoint. Others have reached the same conclusion."

(2) Recently Edsall states, "I have published some results of the estimation of the 'readily eliminable' fraction of the urinary sulphur. There was some reason to believe that this might bear an important relation to liver disease. My results, together with those of Petry and Lang, apparently demonstrate that this fraction of the urinary sulphur is of no clinical importance of any kind.

(3) I have also made a considerable series of estimations of the ratio between the total nitrogen and the ammonia nitrogen of the

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urine in liver disease and in other conditions. This was of some interest, because of the teaching, which has so long been prevalent, that most of the urea is formed (from ammonia) in the liver. My results agree with those of others that have recently mentioned this question, in showing that this ratio has no importance in the diagnosis of hepatic disease, and indeed, it is all but certain that much of the urea is formed elsewhere than in the liver, particularly when that organ is diseased.

(4) Since Strauss referred to some suggestive results from the estimation of the volatile fatty acids of the urine, I have made a series of estimations of these. I have repeatedly found excessive amounts in liver-disease; I have quite as often found them normal; and I have frequently found them much increased, when there was no other indication of even temporary disturbance of the liver." Comparatively little work has been done on the excretion of the volatile fatty acids in various diseases, and more observations would be of value. I do not believe, however, that they will offer much aid in the diagnosis of disorder of the liver.

(5) Strauss has also recently reported some very interesting results from tests for alimentary levulosuria as a means of diagnosing disease of the liver; and Bruining and Ferrannini have had favorable results from the test. My own results in a small series of cases of cirrhosis (6) have led me to believe that the test is of little or no practical value; for levulose did not appear in the urine of any of these cases in amounts sufficient to give a frank reduction of Fehling's solution or to cause distinct fermentation, and even the delicate Seliwanoff reaction was absent in half the cases. Moreover, this test is quite often positive in this slight degree in other conditions; then, too, it has no further experimental basis than the fact that Hans Sachs has shown that when the livers of frogs are removed, these animals do not assimilate levulose. It has never even been indicated that levulose is assimilated in frogs by the liver alone, or that this is so in any other animals. It is, indeed, extremely probable that other organs have a large share in this; hence, it is likely that liver-disease has no constant or reliable relation to a disturbance in the assimilation of levulose.

(6) I also began, some time ago, some work on the amidoacids of the urine in liver-disease; but I have not carried this far. It was suggested by the recent work demonstrating the activity of autolysis in liver-substance, and by the well-known relation between acute yellow atrophy, etc., and the excretion of leucin and tyrosin.

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Von Jaksch has recently contributed a few observations related to this question, which are interesting. The matter would repay further study from a purely pathological standpoint, and perhaps from the clinical.

(7) I have made numerous observations concerning urobilinuria, and can only agree with most other observers that it is, at most, suggestive of liver-disease—and then, only when a number of other conditions can be reasonably excluded. The latter is a difficult task; and, further, urobilinuria is often absent in hepatic disease.

It has been quite clearly established that urobilin is in most instances, at least, and in chief part, formed in the intestines by bacterial action. For this reason I have, with the aid of Dr. Fife and Dr. Wile, made a series of about 200 observations of the relations between urobilinuria and the excretion of various enterogenous decomposition products—a question that has hitherto received very little attention. A portion of these observations were made on cases that certainly had disease of the liver. The results indicate that even in the absence of any demonstrable increase in blood-destruction, urobilinuria is not always dependent simply upon abnormal or increased intestinal decomposition-processes. Our results also lead me to think it probable that urobilinuria is commonly due to imperfect alteration of urobilin after its absorption from the digestive tract; and this imperfect alteration is probably due chiefly to disorder of the liver. This view is in accord with the growing opinion that excessive excretion of enterogenous recomposition-products often indicates disturbance in tissue-processes, rather than simply disturbance in the digestive tract. If this view can be demonstrated to be correct, it will indicate that urobilinuria is more directly related to disorder of the liver than is now generally taught; but more definite facts would be needed to give it greater diagnostic importance than it has at present.

A number of observers have recently insisted that indicanuria is often an indication of disorder of the liver, rather than of the digestive tract. It is undoubtedly true that intense indicanuria, with or without urobilinuria, is often seen in liver disease, and frequently when any marked gastrointestinal disturbance is absent. This is, however, an inconclusive fact, and one that offers no important aid in diagnosis.

A fact that has interested me more than this is that I have repeatedly observed, in definite liver-disease, and in chronic alcoholism when any distinctive signs of liver-disease were, as yet, absent,

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that the distillate from the acidified urine persistently gave an intense phenol reaction (with bromine-water), even when there were no noteworthy evidences of disturbance of the stomach or intestines. This intense phenol-reaction is common in infectious fevers and in marked gastro-intestinal disturbances. Except in such conditions, an intense reaction has, in my experience, been generally associated with disease of the liver, or with alcoholism or other conditions that gave rise to a suspicion of liver-disease; and it has frequently been combined with a more or less marked urobilinuria. Herter has shown that liver-substance causes phenol to disappear, and it is also probable that the synthesis of phenol into conjugate sulphates takes place chiefly in the liver. These facts, the results that I have mentioned, and other reasons make it seem probable that phenol may bear some relation to liver-disease that will prove to be of clinical importance. My observations concerning this point are, as yet, very inconclusive. A mere excess of phenol in the urine is certainly not, of itself, in any way indicative of hepatic disease; but there are some features of the excretion of phenol that are, I believe, worthy of further attention in this connection."

Gastric Analyses. Such analyses carefully conducted will enable one to differentiate between liver and gastric conditions and with the physical examinations will usually lead to the recognition of the gastroptosis and the dilatations which cause pain simulating gall bladder affections. It is well known that hyperacidity attends gall-stones. I found constant hyperacidity in two cases in young subjects who had symptoms of cholecystitis, but in whom I could not elicit the antecedent and attending phenomena of cholelithiasis. It occurred to me just as pancreatitis may be caused by hydrochloric acid—so cholecystitis might be induced if the acid could get into the ducts. Experiments conducted to determine this point by Drs. Yates and Pearce showed that in healthy subjects gastric juice could not be forced into the gall bladder from the duodenum.

A. Two experiments—dead dog, pylorus ligated, duodenum below bile duct ligated. Bowel filled with eosin solution containing lamp black in suspension. Forcible manual pressure for several minutes. Result negative. Duct not stained.

B. Same experiment on human cadaver. Result negative.

C. (1) Live dog. Ligation of duodenum 20 cm. below pylorus. Injection of same fluid. Animal killed after five hours. Had not vomited, but was collapsed, powerless and in dying condition when chloroformed. Examination—slight eosin staining at papilla but no extension along duct.

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D. (2) Same experiment, but ligation below ileo-coecal valve. Killed after sixteen hours. Negative.

Notwithstanding these negative results it may be possible, under altered pathological conditions, that hydrochloric acid or gastric juice may get into the bile passages and cause inflammation.

Historical Diagnosis. Reliance placed on the age, sex, habits and other facts of the social history, and of the previous medical history, are essential in the diagnosis of secondary states. A glance at the secondary morbid states explains this statement.

Fallacy. Attention must be called to the fact that the *age* of persons suffering from cholelithiasis, as determined at autopsy or in the operating room, is not that at which the disease began. The age thus recorded is the age when the secondary processes of calculi have taken place—i. e., infection of the biliary passages in which gallstones are present, producing the symptoms which require treatment or cause death.

CASE I. *Acute cholecystitis. Absence of gallstones, severe infection—Operation—Immediate recovery.*

J. R., age 49, married. Resided in Philadelphia.

"Always reckless with eating" as to time, character of food and method of eating. Moderate in use of beer and whiskey. Passed a renal calculus several years ago. Always inclined to constipation and subject to so-called bilious attacks, which were relieved by purgatives.

Nothing further of interest in social, family or previous medical history.

April 4th, 1902, partook of a supper of indigestible food. April 5th, 4 A. M., seized with severe pain in epigastrium and hepatic region. His physician found him with pain, tenderness over region of gall bladder, a temperature of 101° and pulse 106. No nausea, vomiting or movement of bowels.

Pain continued during the day, for which morphia was taken. Unable to secure a movement of the bowels throughout the day.

April 6th. Fairly quiet night under influence of morphia. Temperature 100°; pulse 104. Pain increasing; abdomen very tympanitic, greatest tenderness over gall bladder region. 4 P. M., temperature 103°, pulse 112. Bowels moved for first time, after high enema. 5 P. M., rigor, pain continued. 8 P. M., rigor repeated; temperature 103.6°, pulse 116.

April 7th. Poor night; moderate collapse; temperature 101°, pulse 116. Sweating; great tenderness over epigastrium and gall

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bladder. Palpable tumor in gall bladder region. Seen by Dr. Musser. Diagnosis, acute cholecystitis. 12 M., temperature 101.4°, pulse 108. Nausea. No bowel movement. Otherwise same. Urine contained bile pigment; otherwise normal. 5 P. M., temperature 102°, pulse 116. Much pain. Operation declined. 11 P. M., temperature 101.9°, pulse 124. Respiration 22. Pain, nervous and restless.

April 8th. Very restless during night; very little sleep. Six stools, thin, yellow. Nausea. Temperature 101.2°, pulse 110. Some perspiration during morning. Headache and backache. Pain and tympany. 2 P. M., temperature 102°, pulse 98. 5 P. M., temperature 105°, pulse 120. Leucocytosis 12,000, Backache and headache. Urine scanty and high colored. 8 P. M., temperature 103.3°, pulse 118. Thin, black stools during evening. Local conditions same.

April 9th, 4 A. M., temperature 99.2°, pulse 92. 8 A. M., temperature 102°, pulse 102. Pain continues. Tumor distinct. 12 M., temperature 101.2°, pulse 96. Headache. 3 P. M., local conditions more aggravated. Temperature 101.3°, pulse 100, respiration 28. Mild delirium; very short of breath. 9 P. M., delirium increased along with other evidence of toxaemia. Temperature 103°, pulse 108, respiration 26. Throughout day several stools. Owing to manifest increase of toxaemia and no relief to local symptoms, consent to operation, which Dr. Martin joined in advising, was given. Operation at 1 A. M. by Dr. Martin. Swollen, oedematous gall bladder surrounded by recent peri-cholecystitis. Distention due to enormous amount of sero-purulent fluid. No gallstones. Drainage. Immediate relief (see chart No. I.).

CASE II. *Cholecystitis* and *Cholangitis* in *course* of *Typhoid Fever.*

February, 1903. At the third week in decline of the fever of a moderately severe attack of typhoid fever, without any cause, increase of temperature as per chart No. II. At end of four days I saw the patient in consultation. No unusual symptoms. Slight nausea. Tongue furred. Marked, but not deep icterus. Tenderness of gall bladder which was palpable. Liver not enlarged. Recovery in ten days.

CASE III. *Typhoid Cholecystitis in Convalescence. Operation.* Recovery.

March, 1903. Seen with Dr. Rehfuss. Patient aged 55. Married; female. Typhoid fever of six weeks' duration. Four days

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after temperature normal, seized with pain and vomiting. In afternoon, chill, temperature rose as per chart No. III. Seen by me on third day. Tympany. Tenderness in region of gall bladder. Pulse rapid and feeble. Constant vomiting. Bowels opened freely.

Physical examination indicated swelling and greatest tenderness between end of ninth rib and umbilicus. Rigidity of right rectus marked. Appendicitis excluded because of history and location of pain and rigidity. Perforation excluded because of time in course of disease, because of absence of shock and sudden pain. It was evident localized peritonitis was advancing rapidly to general. Dr. Martin concurred in the diagnosis and operated four hours after my visit, when pulse was 160; vomiting constant; tympany great. Very extensive peritonitis about liver, gall bladder and in right upper quadrant; gall bladder enlarged and distended. Opened, drained, with prompt recovery, as indicated by the chart.

CASE IV. *Typhoid Fever, Cholecystitis, Acute Pancreatitis.* Death.

January, 1903. The patient was desperately ill with typhoid fever for six weeks. The fever did not subside except for forty-eight hours. A recurrence of fever with chills, as the chart (No. IV) indicates was believed to be due to ugly bed sores and suppuration from hypodermoclecis abscesses. There were no signs of abdominal disease. One day, after slight exertion, turning to drink, she died suddenly.

At the autopsy, suppurative cholecystitis without gallstones, and acute hemorrhagic pancreatitis. The great interest is in the sequence of pancreatitis upon typhoid cholecystitis.

CASE V. *Cholecystitis in Course of Typhoid Fever.* Recovery.

1901. Seen with Dr. Taylor and Dr. Girvin. The patient, a woman, aged 45, was ill with typhoid fever when on the twenty-fifth day the temperature arose, pain, rigidity and tenderness in the gall bladder region was found. A large tumor the size of a large orange, movable with respiration and on palpation tender, filled region between normal gall bladder site and umbilicus. The local symptoms were very severe for ten days, but gradually subsided, the temperature (as per Chart V) declining with the lessening of abdominal symptoms.

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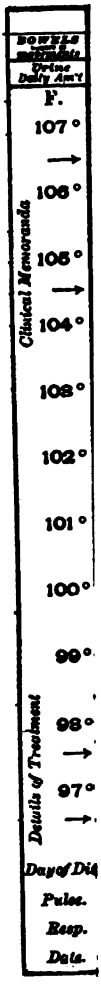

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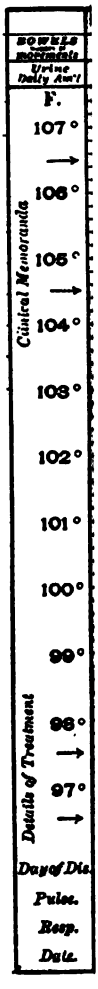
Case II.—



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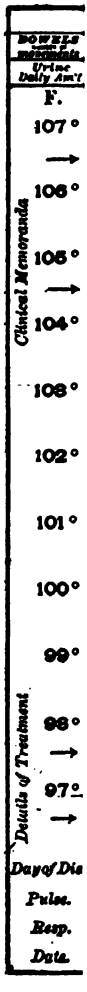
Case III.—C



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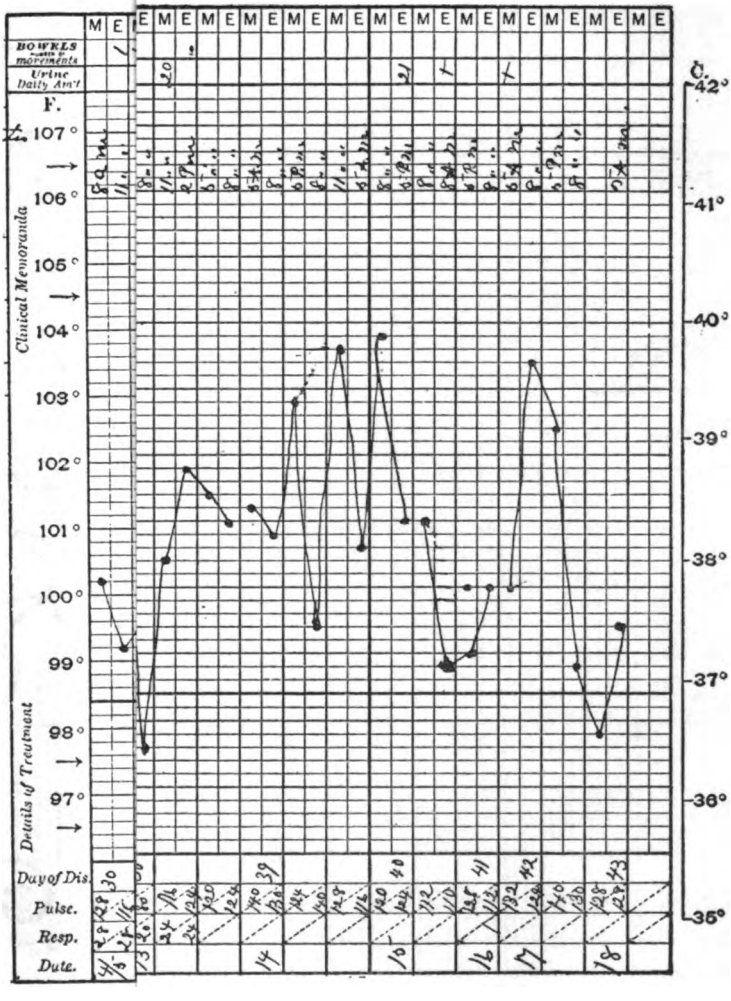
Case IV.—om acute hemorrhagic Pancreatitis.



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THE MEDICAL AND SURGICAL ASPECTS OF THE DISEASES OF THE GALL BLADDER AND BILE DUCTS.

THE DIFFERENTIAL DIAGNOSIS OF DISEASES OF THE GALL-BLADDER AND BILE DUCTS.

BY GEORGE EMERSON BREWER, M.D.,

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During the professional experience of the writer, the surgery of the gall bladder and ducts has passed through three distinct phases; the first, in which little or no attention was paid by surgeons to diseases of these organs, as evidenced by the fact that the entire subject was practically ignored by surgical writers; the second, in which surgeons occasionally operated for the late sequelae of these conditions, as in empyema of the gall bladder, intra-abdominal abscess, ulcerative or gangrenous cholecystitis, impacted calculus in the common duct, or intestinal obstruction from the presence of large concretions which had ulcerated through the gall bladder into the alimentary canal; and third, the gall bladder surgery of the present day, in which surgeons not only seek to relieve the dangerous sequelae of neglected disease, but by early recognition and timely intervention seek to eradicate the disease at a period when it can be accomplished with relative safety, and thereby avoid the serious septic and cholaemic terminal conditions in which operative procedures are attended with great risk and a very considerable mortality.

The same sequence of events has been observed in the development of the surgery of the female pelvic organs, the kidney, the vermiform appendix and the alimentary canal; the progress in each instance being due to a better understanding of the pathology and general behavior of the various diseased conditions, a gradual improvement in operative technic, and the ability to arrive at an accurate diagnosis at an early period. It is the last of these factors in the surgery of the gall bladder and ducts, to which attention will be directed in this communication.

In the early part of the first period referred to above, but little was accurately known regarding the nature of the various affections

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of the biliary passages, which gave rise to the clinical symptoms of jaundice, colic, vomiting, pain and tenderness in the right upper quadrant of the abdomen; practically all cases being clinically classified as catarrhal jaundice, gallstones or cancer, and although isolated cases had from time to time been reported as having received surgical treatment, notably those of Bobbs, Marion Sims and Langenbuch, these affections were generally regarded by the profession as belonging exclusively to the domain of the practitioner of internal medicine.

In the latter part of this period the importance of inflammatory conditions of the gall bladder began to be recognized, and, as in the case of the vermiform appendix, the relationship between these and the localized and spreading forms of peritonitis appreciated.

The second period began with the publication by Courvoisier of his masterly work on the pathology of diseases of the biliary passages, in which he reports not only his own sixteen cases and the twenty-seven cases of Kocher, Kappeler, Socin, Krönlein, Fritzche, Kauffmann, Kunz and Niehaus, but gives in addition a complete review of all the literature of the subject, and by a careful analysis of an exceedingly large collection of clinical reports and autopsy findings, is able to establish certain facts bearing upon the pathology and symptomatology of these conditions, which have formed the framework of our present knowledge of the subject.

The facts presented by Courvoisier in this work clearly demonstrated to the profession that in the great majority of instances these affections could only be relieved by surgical intervention. The result of this publication, therefore, served to awaken a very general interest among surgeons in all parts of the world, and in the decade which followed many new and ingenious operations were devised and successfully carried out; much was added to our knowledge regarding the pathology and general behavior of these diseases, gained chiefly by accurate observation of the conditions found at the time of operation; and by a careful comparison of these findings with the clinical history observed before operation, many additional facts contributing to a more accurate diagnosis have been established.

Encouraged by the success which attended the surgical treatment of these affections, which contrasted sharply with the frequent failure of the expectant or purely medical method of treatment, surgeons began to advise and carry out early prophylactic operations, especially in those conditions caused or aggravated by the

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presence of calculous formation. This advance brought the profession to the third period.

The tendency in these early operations, as in those upon the appendix and kidney, is to greatly reduce the sufferings and dangers which accompany the more advanced stages and sequelae. Obviously these advantages can not be generally secured until the ability to arrive at an early special diagnosis is acquired by the profession at large, and when, likewise, the unreasonable prejudice against early and safe prophylactic operative procedures is overcome. When these two conditions are realized a fourth and ideal period in the development of gall bladder and duct surgery will have arrived.

As it is only by a comparison of carefully recorded clinical histories with the findings at operation or autopsy, that substantial progress has been made in diagnosis, and as data bearing on this subject are constantly being furnished from reliable sources, it seems desirable from time to time to review the current literature and to present in concise form the important facts bearing upon this subject. This has been creditably done in the past by Robson, Waring, Kehr, and others. Perhaps the most important contribution to the subject since the work of Courvoisier is the communication of Prof. Hans Kehr entitled "Anleitung zur Erlernung der Diagnostik der einzelnen Formen der Gallenstein-Krankheit," published in 1889, in which the writer presented to the profession a report of his four hundred and thirty-three operations on the gall bladder and ducts. In these reports the symptomatology of each case is carefully recorded, as are the actual pathological conditions found at operation or by autopsy, and his work undoubtedly furnished the most important collection of reliable data upon the diagnosis of these diseases which had then appeared.

Stimulated by a perusal of this interesting monograph and actuated by a desire to present in the form of a simple chart for the use of students the essential facts in diagnosis of these conditions, the writer in 1900 undertook a review of reports which had appeared up to that time, giving symptomatology and accurate anatomical findings, together with the statements contained in the treatises of the best acknowledged authorities on the subject, to which was subsequently added the facts gleaned from a comparatively limited personal observation.

This chart, with a brief explanatory paper, was presented by invitation to the Surgical Section of the Buffalo Academy of Medicine on November 5, 1900, and has since been used by the writer in his section teaching in the College of Physicians and Surgeons.

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Since the publication of that chart a number of important communications on the subject have appeared, notably by Kehr, Richardson, Murphy, Ochsner, Mayo, Ferguson, Riedel, Allen, Stockton and others, and although the writer finds no reason to alter the chart in any material respect—for he believes that it still represents an accurate though perhaps incomplete statement of the typical symptoms and signs of the various pathological processes—yet a number of exceptions to the typical clinical types of diseases must be described and the results of the more recent contributions added. This, and a statement of the facts upon which he based his original conclusions regarding the symptomatology, will furnish the subject matter of the present communication.

A glance at the chart will show that the diseases ordinarily encountered in the gall bladder and ducts may be divided into three main classes—calculous disease, inflammatory disease and new growths.

Calculous disease:—Calculous disease of the biliary passages is of frequent occurrence, according to Riedel and Kehr, being found in ten per cent. of all adult autopsies. (The writer found it twelve times in one hundred subjects examined in the dissecting-room of the College of Physicians and Surgeons.) In perhaps ninety-five per cent. of all cases it gives rise to no symptoms (Kehr). In the remaining five per cent. it occasions symptoms which vary in intensity and importance from a slight transitory jaundice or discomfort in the right hypochondriac region to a rapidly fatal septic peritonitis.

One or more stones in a healthy gall bladder with patent ducts, produce, as a rule, no symptoms, and under these conditions the only physical signs present are those of a tumor of the gall bladder, caused by the number or size of the calculi.

Tumor of the gall bladder, present under the conditions enumerated above, from the large size or number of gallstones, or from an accumulation of fluid, is usually more easily defined than in inflammatory conditions, on account of the absence of a pericystic exudate and of rigidity of the abdominal wall.

The presence of a number of stones in a gall bladder has occasionally been recognized during palpation by a *bruit* which, according to Petit, resembles the rubbing together of nuts in a bag. This observation has also been confirmed by Courvoisier, Ferguson and others.

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D DUCTS.

	Pathological	Liver.	Spleen.	Ascites.	Remarks.
I. Calculous Disease.	(a) Ston gall bl free.	Not enlarged	Not enlarged	No.....	Generally discovered by accident; often unrecognized.
	(b) Ston gall bl duct te structe	Not enlarged	Not enlarged	No.....	All symptoms promptly relieved as soon as obstruction is removed.
	(c) Ston cystic	Not enlarged	Not enlarged	No.....	Hydrops of gall bladder; often unrecognized.
	(d) Ston duct.	Frequently enlarged.	Not enlarged	No.....	Diagnosis extremely difficult; symptoms generally due to coexisting cholangitis.
	(e) Ston duct; structi	Not enlarged	Not enlarged	No.....	Symptoms rapidly disappear when stone passes papilla.
	(f) Ston duct, chronic	May be enlarged during attack.	May be enlarged from pressure of stone on vein.	No.....	"Fièvre intermittente hépatique" of Charcot resembles malaria; all symptoms disappear during interval.
	(g) Ston duct, chronic	Enlarged ...	May be enlarged.	No.....	Condition may remain for many years; may only be jaundice with digestive disturbances and loss of weight; history of previous attacks (?). Ascites may be present from pressure of large stone or possibly from hydræmia.
II. Inflammatory Disease.	(a) Cho acute.	Not enlarged	Not enlarged	No.....	Tenderness over gall bladder; tendency to recurrence; generally associated with stones in gall bladder.
	(b) Chol	Not enlarged	May be enlarged (sepsis).	No.....	May follow typhoid or other septic diseases; onset often sudden; rapid development of severe symptoms resembling appendicitis; may be necrosis of walls of gall bladder with perforation, local or general peritonitis.
	(c) Ch chronic of gall	Not enlarged	Not enlarged	No.....	Frequently follows acute cholecystitis; occasionally becomes quiescent, presenting practically no symptoms.
	(d) Cho previo and co bladde	Not enlarged	May be enlarged (sepsis).	No.....	Generally tenderness over gall-bladder area, but no tumor; local peritonitis; diagnosis often extremely difficult.
	(e) Chol atic a ducts.	Enlarged ...	Enlarged (sepsis).	No.....	Often follows severe infections of gall bladder; generally associated with stones in common or hepatic ducts; severe sepsis; generally fatal in virulent infections (streptococcus).
III. New Growths.	(a) Car bladde	Enlarged late in disease.	May be enlarged late (pressure on vein).	Present late.	Digestive disturbances, progressive loss of weight and asthenia; cachexia; rapidly fatal.
	(b) Tum duct.	Not enlarged	Not enlarged	No (?).....	Very rare; both benign and malignant growths have been reported; diagnosis difficult.
	(c) Tum or com	May be enlarged.	Not enlarged	May be present late.	Very rare; diagnosis difficult.
	(d) Tu boring ducing structi duct.	Enlarged ...	May be enlarged late.	Present late.	Malignant tumors most common; chronic interstitial pancreatitis from previous infection of biliary passages may remain after cause has disappeared; enlarged portal glands; Hodgkin's disease.

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Occasionally a stone can be distinctly palpated, as in the case reported by Lessdorf, in which he was able to feel the stone through the separated muscles of an umbilical hernia.

The writer has recently observed a case in which one could grasp a distended gall bladder through an abnormally relaxed but otherwise normal abdominal wall and easily appreciate a number of stones, one of which appeared to be as large as a walnut.

If a calculus is temporarily impacted in the neck of the gall bladder or cystic duct, pain is produced, often with nausea, vomiting and localized tenderness, the latter best appreciated, according to Murphy, by hooking the flexed fingers beneath the right costal border and instructing the patient to take a deep inspiration. The pain of an impacted gallstone varies in degree from a slight feeling of discomfort to a colic, the intensity of which is equalled only by the pains of the second stage of labor. The attack often ceases suddenly with the occurrence of vomiting, which by relaxing the spasm, allows the calculus to fall backward into the bladder. Muscular rigidity and fever are absent unless inflammation is present. This is an exceedingly common manifestation of calculous disease, often unrecognized and frequently diagnosticated gastralgia, intestinal colic, or acute indigestion.

If, however, the stone becomes permanently impacted in the cystic duct, or if the duct becomes permanently obstructed in any other manner, as by a new growth or cicatricial contraction, there occurs a gradual increase in the size of the gall bladder by an accumulation of fluid within the cavity. In the absence of infection, this fluid is sterile and consists of a thin mucus secreted by the mucous membrane, which gradually distends the gall bladder, often to an enormous size, giving rise to no discomfort excepting that produced by pressure from the size of the tumor. In this condition of hydrops of the gall bladder, the walls of the viscus become extremely thin, the fluid is at first bile stained, and later becomes cloudy and often opalescent.

A tumor of this character develops slowly, is situated immediately behind the abdominal wall below the free border of the ribs on the right side, and appears continuous with the liver at a point opposite the junction of the ninth rib with its cartilage. It develops downward and somewhat toward the median line; it moves with respiration and may permit a lateral pendulum-like motion on palpation. It is generally smooth, of even oval contour, and its consistence may be soft, hard, fluctuating or elastic. The shape of the tumor is

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variable; it may be round, elongated, pear-shaped, or reniform (Riedel). A change in the size and shape of a gall bladder tumor is occasionally observed, and is probably due to dislodgment of a previously impacted stone, or to valve-like obstruction in the cystic or common duct. Petit reported a case in which it could be emptied by external pressure. Goldwitz and von Lucke have reported cases in which the tumor was apparently due to paralysis from over-distention, similar to that so often observed in the urinary bladder. It may be of interest in this connection to note that the gall bladder has occasionally been found near the median line (Kehr) or under the free border of the ribs of the left side, as reported by Raymond and Carl Beck. Congenital absence of the gall bladder has been once observed by the writer, and Courvoisier has referred to a case in which it was apparently absent, but in reality was deeply embedded in the substance of the liver.

The passage of a stone through the cystic duct may give rise to no painful sensation. Lawson Tait, however, expressed the belief that it causes far more pain than when passing through the large common duct, and Kehr has made a similar statement.

Considerable controversy has arisen regarding the pain caused by the passage of a stone through the healthy cystic and common ducts. It was formerly held that the transit of such a stone was practically the sole cause of biliary colic, and Murphy still believes that true colic, as distinguished from steady pain, discomfort and tenderness is invariably due to a moving foreign body. Kehr and a number of other authorities, however, hold that pain in gall bladder or duct disease is practically always the expression of an inflammatory process. The fact that ninety-five per cent. of all cases of calculus present no symptoms, and the fact also that a majority of the calculus cases that come to operation present, in addition, signs of inflammation, would strengthen this view.

Ferguson reports a series of experiments on this point made with probes, bougies and water pressure on a case of cholecystostomy with biliary fistula—and concludes that pain may be caused by pressure and spasm, as well as by inflammation.

As the condition of the biliary passages under these circumstances can hardly be assumed to be free from infection, his conclusions can not be accepted as proving absolutely the non-inflammatory origin of biliary colic. It is probable that the presence of a stone or other foreign body in an infected duct produces colic more frequently than either condition alone. Without attempting to settle

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the exact etiologic factor in the production of pain, practically all observers agree that acute paroxysmal pain in the upper abdomen is the most constant and characteristic symptom of cholelithiasis. Riedel,[1] in a recent publication states that of one hundred cases of epigastric colic (Magenkrampfen) ninety-seven have gallstones or adhesions of the gall bladder, two may have ulcer or cicatrices of the stomach, and one spasm of the pylorus.

The diagnosis of stone in the hepatic duct is often very difficult. Courvoisier reports fifty-two cases with fairly accurate histories; in four there were no symptoms, in twenty-two pain was present, without any regular type, and occasionally accompanied by digestive disturbances and vomiting. In sixteen there were enlargement of the liver and tenderness. Thirty-five had more or less jaundice (in six it was distinctly absent). In nineteen there was fever of an intermittent type. In fifteen there was in addition a suppurative cholangitis.

The diagnosis of stone in the common duct is less obscure; the three most important symptoms are jaundice, pain, and fever. Practically all observers regard jaundice as the most constant and reliable symptom of obstruction of the common duct. When this symptom is due to calculus the diagnosis is comparatively easy: when due to other forms of obstruction it is often extremely obscure. Acute temporary common-duct obstruction from stone produces a rapidly developing jaundice which as rapidly subsides when the stone passes into the duodenum. When the stone becomes impacted in the region of the papilla the jaundice is progressive and often becomes extreme. If, however, the dilatation of the duct above the obstruction, from an accumulation of bile, causes the stone to become dislodged, and it floats upward in the dilated common, cystic or hepatic ducts, the obstruction is temporarily removed, the bile again flows into the intestine, and the jaundice disappears, only to recur when the ducts contract around the stone or it is again impacted at the papilla.

In one of his later publications Kehr[2] states that jaundice is absent in thirty-three per cent. of his cases of stone in the hepatic and common ducts, due largely to the absence of infection. He believes that here as in other portions of the biliary tract, stones

[1] Riedel, Pathogenese, Diagnose und Behandlung des Gallensteinleidens, 1903, Jena.

[2] Ein Rückblick auf 720 Gallenstein Laparotomien unter besonderer Berücksichtigung von 90 Hepaticusdrainagen.

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may remain latent for long periods of time, giving rise to symptoms only when an inflammatory complication is added. Murphy[1] on the other hand states that while jaundice may be remittent it is never completely absent in stone in the hepatic and common ducts. It is difficult to reconcile these divergent statements emanating as they do from equally accurate observers.

Pain in common-duct obstruction strongly points to stone. In eighty cases of calculus in the common duct reported by Courvoisier, pain was a prominent symptom in fifty-one; absent in ten; and unrecorded in nineteen.

In seventy-nine obstructions from other causes it was present in only nine instances.

In intermittent obstruction from a floating stone, it is generally more acute during the period of obstruction. It is then often paroxysmal in character, radiates to the back and shoulder, rarely is it constant and fixed in one locality. Tenderness is generally more marked nearer the median line, and slightly lower than when the gall bladder is the seat of trouble.

Fever is less constantly present, but when present is generally of a characteristic type. It was noted in nineteen of Courvoisier's cases, while in seventy-four obstructions from other causes it was present but seven times. It is often intermittent in character, and is accompanied by chills and profuse sweats. This type of fever was described by Charcot as *fièvre intermittente hépatique,* and its similarity to malaria pointed out by many other observers. When present with jaundice and colic, it is almost pathognomonic of stone in the common duct. Although believed by many to be reflex or due to the absorption of bile, most modern observers agree with Schuppel in regarding it as of septic origin, as the presence in these cases of a certain degree of cholangitis is practically constant.

When the flow of bile into the intestine is hindered the urine will be dark from the presence of pigment; when completely obstructed, the stools will be clay colored.

Tumor of the gall bladder is generally absent. It has, however, been occasionally observed. Enlargement of the liver is frequent and due to the dilated intra-hepatic ducts or to an extension upward of the cholangitis, in which case there will be tenderness over the liver, and enlargement of the spleen. Ascites is present only when the obstructing stone is large and presses on the portal vein.

[1] The Diagnosis of Gall Stones, Med. News, May 2, 1903.

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Inflammatory disease:—Inflammation of the gall bladder or ducts is present in the vast majority of patients who apply to the surgeon for relief.

Infection of these organs arises generally from an upward extension from the intestine, due to an abnormal patency of the duodenal orifice; occasionally from some general septic disease; very rarely from trauma. Thus Courvoisier in fifty-five cases of empyema of the gall bladder found cholelithiasis in forty-one; in two it was thought to be due to trauma, in two to general sepsis, in one to typhoid fever. Inflammation of these organs may be conveniently divided into two general classes—the mild and the severe infections; the former due to the colon or typhoid bacillus, the latter to the streptococcus or some other equally virulent organism. In the great majority of instances, cholelithiasis has preceded the inflammation and prepared the way for it.

The symptoms of cholecystitis are pain, localized tenderness, fever, and occasionally the presence of a tumor of the gall bladder.

In a mild infection of the organ with the ducts open, insuring free drainage into the bowel, these symptoms may be wanting. If the cystic duct becomes obstructed from stone or swelling of the mucous membrane or pressure from an inflamed lymph node, colicky pains occur, which may radiate to the back and shoulder; vomiting is generally present during the period of obstruction; there are usually also slight fever and general malaise which disappear with the pain when the obstruction is relieved. Unless the gall bladder be small or deeply seated under the right lobe of the liver, a sensitive tumor may be felt during the continuance of the obstruction. These symptoms frequently subside spontaneously, but the tendency to recurrence is marked.

If chronic obstruction of the cystic duct occurs, empyema of the gall bladder results, giving rise to symptoms of varying severity, according to the virulence of the infecting agent and the resistance of the individual. This condition may also exist with open ducts, as evidenced by Courvoisier's statistics, in which he reports the ducts free in eleven of forty-one recorded cases of empyema. The pain and fever may be wanting, the only symptoms being the presence of a tender tumor in the gall bladder, or, in cases of a small or contracted gall bladder, only a local tenderness or muscular rigidity. In the severer cases the pain is acute, paroxysmal, and radiating, the fever is high and accompanied by chills and vomiting. A local peritonitis may be present and give rise to intra-abdominal abscess, a

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condition often resembling appendicitis. Murphy has recently called attention to a rare form of infective cholecystitis, with or without the presence of calculus, in which the symptoms are only those of a severe intermittent fever with chills and great prostration. There is no pain and no jaundice, only a slight tenderness over the gall bladder region. These cases on operation may present only a mild oedema of the gall bladder wall; the bile presents no gross changes. The cases are completely relieved by drainage of the gall bladder.

In the more virulent infections the symptoms often develop with great rapidity, and are accompanied by marked prostration and a rapidly developing sepsis. Perforation of the gall bladder with a fulminating, rapidly fatal, septic, general peritonitis may occur. In a number of such cases reported by Richardson, diagnosis was impossible, the symptoms suggesting only a rapidly spreading peritonitis or an intestinal obstruction without localizing symptoms.

Jaundice is absent in cholecystitis unless the tumor of the gall bladder or cystic duct or an enlarged lymph node presses upon the common duct.

In inflammation of the common or hepatic ducts, however, jaundice is often present in addition to the pain and fever, but unless accompanied by stone or complete obstruction from other causes is seldom of a severe type. In the more virulent infections of the common and hepatic ducts, the process extends rapidly to the intrahepatic branches and gives rise to general sepsis, often without other symptoms, leading, unless speedily relieved by surgical means, to multiple hepatic abscesses and death. This condition is practically always accompanied by the presence of foreign bodies in the ducts or gall bladder. In seventy-four cases analyzed by Courvoisier fifty-seven had calculi, seven ascarides, and three echinococcus.

New growths:—While new growths of neighboring organs not infrequently produce symptoms referable to gall bladder or ducts by external pressure or direct extension, primary new growths in these organs are comparatively rare.

The gall bladder is most frequently affected, and in the great majority of instances the tumor is carcinoma. Sarcoma and adenoma have been reported; the latter, according to Zenker, may undergo carcinomatous degeneration.

Carcinoma was observed, according to Courvoisier, in seven of two thousand five hundred and twenty autopsies. A study of Musser's report, however, published in 1889, gives one the impression that the disease is somewhat more frequent. Three-fourths of

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the cases were in women, the decade furnishing the greatest number being between fifty and sixty. In one hundred cases analyzed by the author, pain was present in sixty-two. It was usually observed in the right upper quadrant of the abdomen, but was often referred to the shoulder, back or epigastric region. In a number of instances it was paroxysmal and presented the ordinary characters of biliary colic. Vomiting was present in thirty-nine cases, a palpable tumor in sixty-eight. Jaundice was recorded in sixty-nine patients, ascites in eighteen. Kehr states that the last two symptoms are always due to involvement of the neighboring lymph nodes, causing pressure on the duct or portal vein. The temperature was generally normal or subnormal, fever being reported in but eighteen cases.

As sixty-nine of these cases had calculi and as absence of calculi was noted only in three instances, it is probable that many of these symptoms were due to the calculi or to an associated cholecystitis or cholangitis.

The only reliable sign which can be detected early is the presence of a hard, irregular tumor of the gall bladder. The diagnosis is exceedingly difficult; in only four of Courvoisier's one hundred cases was the nature of the disease determined during life. The disease is rapidly fatal; in fifty-three cases followed to the end, death occurred in all within nine months from the first characteristic symptom.

Both benign and malignant tumors occur in the bile ducts. Of the benign growths adenomata and papillomata have been reported by Robson; the latter, he states, occasionally undergo carcinomatous changes. Carcinoma of the bile ducts is generally of the columnar cell variety. It occurs with equal frequency in males and females. It is less often associated with calculi than malignant disease of the gall bladder. Of thirty-four cases collected by Musser and Rolleston, gallstones were present in one-half the cases only. Of Musser's eighteen cases, fourteen occurred in the common duct, three at the duodenal orifice, three in the hepatic, and one in the cystic. The gall bladder was distended in eight, atrophied in one. Stones were present in seven, and suppuration in two. Pain was a prominent symptom in twelve cases: it was frequently paroxysmal and was often referred to the epigastrium. Vomiting occurred in nine instances or one-half the cases. A palpable but small tumor was observed in eight cases.

Growths occurring in the cystic duct give rise at first to a distention of the gall bladder; those in the hepatic and common ducts

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to jaundice, and at a later period to distention of the gall bladder and enlargement of the liver. The jaundice is progressive, and in five cases reported by Delafield was the first symptom. Septic cholangitis may develop especially in growths at or near the ampulla of Vater and give rise to *fièvre intermittente hépatique.* Intermittent jaundice has rarely been observed in such cases, probably due, as suggested by Harrimann, to sloughing of a part of the obstructing mass, allowing a temporary flow of bile into the intestine; or, as reported by Courvoisier, a pedunculated tumor near the papilla may act as a valve and occasionally permit the passage of bile.

Chronic obstruction of the bile ducts from outside pressure is of frequent occurrence. The causes of this condition in the order of their frequency being, carcinoma of the head of the pancreas, chronic interstitial pancreatitis (a condition of sclerosis of the pancreatic tissue frequently limited to the head of the gland—generally due to an infection carried to the gland by the canal of Wirsung, and often associated with inflammatory conditions of the biliary passages), tumors of the pylorus or duodenum, cysts of the pancreas, enlarged lymph nodes and cicatricial contractions. As would be expected, such pressure when limited to the cystic duct gives rise to a gall bladder tumor (hydrops); when it involves the hepatic and common ducts it gives rise to a progressively increasing jaundice without pain or fever, distention of the gall bladder, enlargement of the liver and later ascites.

In conclusion the writer feels that he cannot do better than to quote with some slight modifications the last few paragraphs from his previous paper regarding the significance of the three chief symptoms occurring in diseases of the gall bladder and ducts.

Pain:—The occurrence of repeated attacks of acute paroxysmal pain, in the upper right quadrant of the abdomen, strongly suggests a lesion of the biliary passages. This suggestion is accentuated if the attacks occur at night, or during fasting, and are accompanied by vomiting and fever. If the pain radiates upward to the back and shoulder, and if an area of tenderness exists under the free border of the ribs, the diagnosis is still more probable.

If in addition to the pain we have a palpable tender tumor under the lower border of the ninth rib, or if there exists a point of tenderness in the same location, with moderate spasm of the upper half of the rectus muscle, in all probability the case is one of cholecystitis. If, on the other hand, there is jaundice but no gall bladder tumor, we probably have to do with stone in the common duct.

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Other conditions giving rise to acute pain in the upper abdomen, to be excluded, are, first, gastric ulcer, in which the pain and tenderness are more generally located in the epigastric or left hypochondriac region, and in which fever, as a rule, is not present; appendicitis, in which vomiting and fever may also be present, but the pain and tenderness are usually located in the right lower quadrant of the abdomen; renal colic, in which the pain originates in the flank and extends downward along the ureter to the testicle, which may be retracted, and which is often accompanied by vesical irritation and hæmaturia; Dietel's crises in cases of movable kidney, which are generally promptly relieved by assuming the recumbent posture or replacing the dislocated organ; the gastric crises of tabes, in which fever is absent, and although the vomiting is present, there is no characteristic point of tenderness. These tabitic cases also show an absence of the patella reflex, the presence of pupillary symptoms, sensory disturbance and ataxia in the extremities. Occasionally, pain in this region, strongly simulating biliary colic, will be caused by the presence of inflammatory adhesions in the region of the pylorus and duodenum, causing a narrowing of the canal with dilatation of the stomach. Aneurism of the hepatic artery (Riedel), interparietal hernias, pancreatitis, intestinal obstruction, or the early pain of a local peritonitis from other causes, has given rise to difficulties in diagnosis; and lastly, syphilitic hepatitis may present pain and other symptoms almost identical with those generally found in calculus disease of the biliary passages.

Tumor:—A tumor in the right hypochondriac region, which develops slowly and is preceded by a history of cholelithiasis; which is round, oblong, or pear-shaped, with a smooth convex surface, elastic or fluctuating; which lies immediately under the abdominal wall below the ribs and near the outer margin of the right rectus muscle; which moves with respiration; which allows a certain amount of lateral pendulum-like motion on account of its attachment above; which cannot be made to disappear like a movable kidney under the ribs; and which is not accompanied by pain and fever; is in all probability a gall bladder distended with mucus (hydrops). If with such a tumor there is a progressive jaundice, it is probably a gall bladder distended with bile from a non-calculous common-duct obstruction. If such a tumor is sensitive to the touch and is accompanied by fever it is doubtless a gall bladder distended with pus (empyema). If the tumor is ill defined on account of muscular rigidity, if there are acute radiating pain and marked tenderness in

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the right hypochondriac region with fever and leucocytosis, we have generally to do with a cholecystitis with local peritonitis. The presence of a tumor corresponding to the above description, without pain, fever, or jaundice at first, but presenting a hard, irregular surface, is in all probability cancer.

Jaundice:—The occurrence of a mild transitory jaundice unaccompanied by other symptoms suggests a catarrhal obstruction of the common duct (a mild duodenitis from indigestion). The occurrence of a temporary jaundice with colic suggests the passage of a stone through the common duct into the intestine. The occurrence of intermittent jaundice, intermittent colic, and intermittent fever suggests a floating stone in the common duct. The occurrence of continued jaundice, with chills, fever, hepatic enlargement and tenderness, hypertrophy of the spleen and general sepsis, suggests an infective cholangitis. The occurrence of a progressively increasing jaundice, and enlargement of the liver, with a previous history of colic, but without distention of the gall bladder, suggests an impacted stone near the papilla. The occurrence of a progressively increasing jaundice, without pain or fever, but with a tumor of the gall bladder, suggests common-duct obstruction from new growth.

It is also well in this connection to remember the following facts, gleaned from the writings of those most experienced in the surgery of the biliary passages. Gallstones are rarely found in young subjects; according to Schroeder, only 2.4 per cent. occur in individuals under twenty years of age. The same author states that 20 per cent. of all female, 4.4 per cent. of all male autopsies show the presence of calculi in the gall bladder. Ninety per cent. of the women have borne children. Gallstones have been known to escape from the biliary passages into the alimentary canal by ulcerative processes, and to produce intestinal obstruction without giving rise to pain or any other symptom until the evidences of bowel obstruction appear.

In common duct stone, the calculus is found in sixty-seven per cent. of the cases in the duodenal extremity, in fifteen per cent. in the hepatic extremity, and in eighteen per cent. in the middle portion of the duct (Robson).

One-half of all cases of common duct obstruction only are due to stone (Robson).

In seventy per cent. of the cases of obstruction located in the neck of the gall bladder, the pain is referred to the right sub-scapular region; in ten per cent. to the left sub-scapular region; and in

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twenty per cent. to the precordia, strenum, right, sub-clavicular region or neck (Murphy).

The temperature chart in biliary infection is characterized by *angularity* rather than by *curves,* and by more or less prolonged periods of complete intermission (Murphy).

Jaundice is absent in from eighty to ninety per cent. of all operative cases of gall bladder or duct disease.

Jaundice preceded by colic is practically always due to stone; jaundice without pain is practically always due to inflammation or new growths of the ducts or to outside pressure.

The bile in all cases of cholelithiasis should be regarded and treated as an infected secretion.

During the presence of a calculous jaundice, the sudden occurrence of acute epigastric pain, muscular rigidity, nausea, vomiting and collapse, without leucocytosis, strongly suggests acute pancreatitis occasioned by the presence of a stone in the diverticulum of Vater (Murphy).

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THE MEDICAL AND SURGICAL ASPECTS OF THE DISEASES OF THE GALL BLADDER AND BILE DUCTS.

THE ETIOLOGY AND CHEMICAL PATHOLOGY OF GALLSTONES.

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Although the methods of modern surgery have perhaps robbed gallstones of some part of their medical interest by lessening their menace to life and by doing much to prevent their recurrence, gallstone pathology remains a fascinating field for the experimentalist and is not wholly without promise for the student of preventive medicine and therapeutics. It is the purpose of this paper to deal with our present knowledge of the conditions that attend the production of human gallstones, and, pointing out some gaps in this knowledge, to suggest problems for further research.

The well-known variety in gallstones, as regards their chemical constitution and the arrangement of material within the concretions, is in itself an indication that the conditions of stone-formation are not always the same. Thus the cholesterin stone, consisting almost wholly of cholesterin, disposed in radial crystals about a small debris-center, speaks for a very different developmental history from that of the bilirubin-calcium stone containing little or no cholesterin. In the following pages some explanation will be offered for these varieties in chemical constitution.

Origin of the Chief Constituents of Gallstones.

Since cholesterin and bilirubin-calcium are by far the most abundant and regular constituents of gallstones, it is desirable to consider their origin and the conditions attending their appearance as constituents of calculi.

I. *Cholesterin.**

This monatomic alcohol occurs in bile from human fistulae in only

* Outline of Ritter's Method for Estimation of Cholesterin in Bile.

Weighed amount bile is evaporated to dryness on water bath—and sodium alcoholate added. The whole is kept at a gentle boil on water bath for 2 to 3 hours—then alcohol evaporated off. The residue is taken up in water—pure NaCl added,

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low percentage.[1] In bladder bile the percentage is somewhat higher.[2] The greater proportion observed in the cystic bile can almost certainly be attributed in part to cholesterin derived from epithelial cells lining the gall bladder and not to a concentration of the bile from absorption of water.

Of the origin of the cholesterin of the hepatic bile little is known. A part is probably obtained from the blood and it is likely that diseases attended by a considerable increase in the cholesterin of the blood (as in some cases of diabetes) lead to the passage of an excessive quantity of the compound into the bile, but it must be admitted that there is no convincing evidence on this point. There also remains much to be learned as to the origin of the cholesterin found in normal blood. We know that this substance can be obtained from columnar or cuboidal epithelial cells and that it occurs in the central nervous system. Probably it is a normal cleavage product of larger molecules, but its biological significance is still obscure.

When cholesterin is found either in the crystalline or amorphous state in larger or smaller concretions on the floor of the human gall bladder it is commonly assumed that this cholesterin has been precipitated from a bile that is over saturated. In many instances this is doubtless a correct view, but I think it can be shown that many small masses of cholesterin arise in a wholly different way through the aggregation of very small globules of intra-epithelial material. In the gall bladders of patients dying of chronic nephritis and other chronic diseases, are sometimes found numerous small, dark, friable masses of less than pinhead size, which lie in the dependent parts of the bladder. On examining these masses with the microscope they are seen to consist of epithelial elements which have become highly granular and have lost their normal structure through degenerative alterations. This epithelial debris is commonly stained with bile pigment. It does not contain cholesterin crystals. Nevertheless when a drop of concentrated sulphuric acid is added to some

then evaporated. The thoroughly dried residue is placed in filter cap and extracted with pure dry ether in Soxhlets' extractor for 9 hours. The ethereal extract is filtered, ether removed, and the residue, composed of cholesterin, is weighed. To purify, dissolve residue in little hot alcohol, and add water to the solution in small quantities at a time. Cholesterin separates out, and may be filtered, dried and weighed.

[1] Copeman and Winston found .099 per cent., Mayo Robson .045 per cent., Noël Paton and Balfour .062 per cent.

[2] Observations made by Dr. Baldwin in my laboratory indicate that the cholesterin content of human cystic bile is commonly about .1 per cent.

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of this material it gives a characteristic and marked reaction for cholesterin. The amorphous finely divided cholesterin which gives this reaction cannot reasonably be regarded as a precipitate from the bile but is much more likely to be the direct derivative of epithelial cholesterin. The fact that the bile often contains an excess of cholesterin under these conditions is not opposed to this view, for one would expect that the bile would take up the cholesterin of epithelial origin until it has become quite saturated, after which there would be a liability to crystalline separation at any time.

It is probably true that cholesterin is sometimes separated from a saturated biliary solution, owing to some alteration in the composition of the cystic bile which renders the lipoid material less soluble, but it is unlikely that such alterations in the solvent powers of the bile play an important part in the genesis of calculi. The solvent action of the bile for cholesterin depends in some degree on the biliary soaps and fats and especially on the bile-salts. A certain degree of alkalescence to litmus such as prevails in normal bile (human and canine) is favorable to this solution. There is no definite knowledge of any metabolic peculiarity or anomaly in man which leads to a diminished secretion of biliary salts.[1] Nor do we know of significant changes in the concentration of the soaps and fats. The reaction of the cystic bile in this connection deserves more attention than it has received but the opportunities of studying it in fresh human bile are necessarily very limited.

It is claimed by some writers that acid-producing bacteria give rise to an acid reaction of the bile.[2] There is, however, no satisfactory evidence that this occurs. The bile contains no appreciable reducing substances[3] and probably no fermentable carbohydrates.

[1] A vegetable diet is supposed to diminish the bile-salts and a meat diet to increase them. It is uncertain, however, that these physiological factors assume pathological significance. It has also been thought that decomposition (putrefactive or fermentative) of the bile-salts in the cystic bile reduces the solvent action for cholesterin, but Minkowski showed that the cholalic acids thus liberated still possessed solvent action.

[2] Dott. F. E. Halia, Batteri Della Calculosi Biliare Coltivati Nella Bile, *La Reforma Medica*, vol. II. N. 70, 1901. This observer found in filtered and sterilized ox-bile that colon bacilli and typhoid bacilli gave an acid reaction to bile which had been rendered alkaline. He regards these organisms as the specific exciters of cholesterin stones.

The results obtained by Halia do not accord with those obtained by Dr. Dunham on human bile.

[3] This conclusion was reached by Mr. Rettger from a careful study of pig's bile.

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We know also that one organism, the typhoid bacillus, may be the sole excitant of gallstones containing cholesterin although it is not an acid producer in ordinary media. Whether the cystic bile ever has an acid reaction in consequence of a diathetic acid intoxication cannot be positively stated, but there are facts that render this most unlikely. Hence it may be said, that although an acid bile is favorable to the separation of cholesterin there is no evidence at present to justify us in believing that pronounced acidification of the bile is essential to the formation of cholesterin gallstones.

Excessive Cholesterin Production is the Chief Factor in the Production of Cholesterin Concretions.

The view that the cholesterin of gallstones arises from the mucous membrane of the gall bladder is not new. Budd suggested it in 1845, Bristowe revived it in 1887 and Naunyn became its earnest advocate in 1892. The facts that have appeared to speak most strongly for the local origin of cholesterin are two. First is the observation that epithelial cells desquamated from the mucous membrane of the gall bladder soon undergo degenerative alterations attended with the production of new cholesterin, which in time may take on a crystalline form. This accords with the similar observation that degenerating epithelial cells derived from the bronchial mucous membrane in catarrh and putrid bronchitis often contain cholesterin. The occurrence of this substance in old pus and in old cysts also points to a local origin. Secondly, there is the observation, reported by Naunyn, that the administration of cholesterin to a dog was not followed by an increase of this lipoid in the bile. Although it is stated that the cholesterin was absorbed, the experimental conditions appear not to have been wholly satisfactory for testing the question whether an excess of cholesterin in the blood leads to an increased percentage in the bile.[1] We cannot exclude the possibility that there are occasional disorders of nutrition attended

[1] The difficulty in carrying out such experiments is considerable, owing to the insolubility of cholesterin in water and its resistance to saponification. It is impossible to insure prompt absorption from the intestine or from the peritoneum, and intravenous injections of finely divided substance cause death from embolism. We have not succeeded in heightening the cholesterin content of the bile by experiments of this kind, but do not consider our experiments conclusive as to the question at issue.

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with an increase of cholesterin in the blood serum and, hence, with its increase in the bile.[1]

Experiments made in my laboratory by Dr. Wakeman give strong support to the view that inflammatory conditions in the walls of the gall bladder may lead to an increase in the cholesterin of the bile. Dr. Wakeman injected (under aseptic precautions) strong solutions of bichloride of mercury, carbolic acid, ricin, abrin, and diphtheria toxine into the gall bladder of dogs that had fasted for three days. After periods of three to four days the animals were killed. The gall bladder walls were usually much thickened (especially in the bichloride series), and showed considerable proliferation and desquamation of epithelium together with congestion of the vessels of the submucosa. The solids of the bile were diminished in percentage in the bichloride series. The cholesterin of the bile was markedly increased in the bichloride series, in the carbolic acid series and in the ricin series, the change being especially noticeable in the cholesterin content of the solids. The abrin series and the diphtheria toxine series must be regarded as negative, which corresponds to the absence of structural changes in the mucous membrane of the gall bladder. Some idea of these results may be obtained from the following table.

		Injection into dog's bladder of				Dip.
	Normal	$HgCl_2$	C_6H_5OH	Ricin	Abrin	Toxine.
Number of observations,	20	12	7	6	5	8
Amount injected,		.02 to .1 grms.	.15 to .4 grms.	9 to 2 mg	1 to 1.75	.08 to .4 c.c.
Total bile						
% Cholesterin, Average,	.127	.298	.334	.427	.132	.167
% " Highest,	.260	.458	.940	.823	.231	.255
% " Lowest,	.051	.137	.056	.076	.070	.054
% CaO, Average,	.077	.064	.072	.079	.110	.094
% " Highest,	.115	.166	.111	.150	.134	.155
% " Lowest,	.047	.018	.045	.033	.077	.055
Total bile solids						
% Cholesterin, Average,	.438	2.56	1.47	2.54	.628	.795
% CaO, "	.360	.614	.688	.496	.537	.437

Previous to death the dogs were starved three to four days; those receiving injections were killed three to four days after.

The observed increase in cholesterin, which is especially pronounced in the case of the richin series, depends partly on the pres-

[1] It is extremely probable that the converse is also true, and that conditions causing an obstruction to the outflow of the bile lead to an increase in the cholesterin of the blood. This was claimed by Frerichs to be the case. Observations made in my laboratory, but not yet completed, point to the conclusion that this view is correct.

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ence in the bile of cholesterin holding epithelia,[1] partly on an increased solution of cholesterin[2] (also of epithelial origin) in the bile. One would anticipate that under these conditions the bile would become saturated with cholesterin and thus prepare the way for the deposition of cholesterin from the bile, perhaps in crystalline form. Crystals of cholesterin were not observed in any instance among the remains of desquamated epithelial cells in the gall bladder, but these negative results are not surprising if one considers the short duration of the experimental observations.

An increase in the cholesterin in the bile may be observed after slight mechanical injuries to the mucous membrane of the canine gall bladder, after the intra-cystic injection of cultures of human colon bacilli, after phosphorus poisoning and after a prolonged diet of fat. Bacteria are certainly not essental to the production of the catarrhal inflammations which are attended with an increase in biliary cholesterin. I have several times found the bile to be sterile in mercurial and other inflammations excited by Dr. Wakeman.

Cholesterin Content of Human Cystic Bile.

At my request Dr. Helen Badwin has made observations on the cholesterin content of the human cystic bile obtained from more than sixty autopsies. The results of her earlier analyses are given in the following table.

TABLE II.

Showing Cholesterin Content of Human Cystic Bile in Various Conditions (based on 40 autopsies).

Average of all the cases (excluding 8 cases of acute lobar pneumonia and 3 cases with cholesterin stones)	0.13 per cent.
Average in 6 cases of acute miliary tuberculosis (excluding one case with large cholesterin stones)	0.167 per cent.
Average in 12 cases of chronic nephritis	0.20 per cent.
Average in 8 cases of acute lobar pneumonia	0.248 per cent.
Average per cent. solids of bile in 8 cases of acute lobar pneumonia	11.7
Average per cent. solids of bile in 50 cases analysed	11.3

[1] In collecting the bile for analysis the loosely adhering cells were in every case (in both normal and pathological gall bladders) gently removed with a dull spatula and added to the remaining contents of the gall bladders.

[2] From experiments made by Mr. L. F. Rettger at the Sheffield Scientific School it is probable that some general protoplasmic poisons are capable of increasing the cholesterin within the gall bladder. Thus after a period of phosphorus poisoning of 8 days' duration Rettger found the gall bladder of a rabbit studded with masses about the size of a pin-head, which responded to the chief tests for cholesterin. The bile was sterile. In three other rabbits, similarly treated, no such masses were found.

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There are some points connected with these figures that call for brief comment. In order to obtain strictly normal values for the cholesterin of human cystic bile one would be almost wholly restricted to the results found for biles obtained from healthy individuals who have died by accident. The average given in the table (0.13 per cent.) is based on a series of autopsies which include some instances of sudden death by accident, but which also include a large proportion of deaths from the ordinary causes. These autopsies include, for instance, the series on persons with chronic nephritis. There is consequently no doubt that the average obtained is too high for normal individuals, who would probably give a percentage not very far from 0.1. Nevertheless the comparison with the values found in other groups of cases is of interest.

The relatively high percentage (0.20) found for the 12 cases of nephritis is noteworthy and can hardly be regarded as accidental, although its interpretation is not yet clear. Possibly it depends on an increase in the cholesterin of the serum of the blood connected with the existence of widespread arterio-sclerosis in these cases, but it may be due to local conditions in the gall bladders dependent on the colon bacillus infection, which is so common in persons with advanced nephritis. The bile of persons dead of chronic nephritis often contains a dark sediment of very small granules which seem to consist largely of cholesterin and some of which may possibly be the nidus of future gallstones. The high percentages noted in the cases of pneumonia are also of interest, although here again the interpretation of the results is difficult. Possibly the excessive cholesterin is connected with infection of the bile and bile-passages. It would certainly be interesting to know whether the liability to gallstones is greater among persons who have had pneumonia than among those similarly conditioned who have not had the disease.

It is not unlikely that there are temporary infections of the cystic bile which lead to a temporary increase in cholesterin which gradually returns to normal after the subsidence of the infection.

The bile from gall bladders containing cholesterin stones is certainly apt to contain an uncommonly high percentage of cholesterin. Thus in one instance the proportion reached 0.308 per cent., in another 2.42 per cent. On the other hand, where pigment stones are present the cholesterin of the bile may not exceed 0.014 per cent.

NOTE.—The following observations on the solubility of cholesterin in pigs' cystic bile are of some interest. The analyses were made by Mr. L. F. Rettger. Four portions of same bile, fresh and normal, were taken.

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II. *Calcium.*

Our knowledge of the calcium of the bile in health and in disease is rather less satisfactory than that which we possess respecting cholesterin. We know that the calcium content of canine cystic bile is normally from 0.050 per cent. to .090 per cent., whereas the percentage in the blood is considerably lower.[1] We know also that the calcium content[2] of human cystic bile does not normally differ

a. 100 c.c. unfiltered; amount of cholesterin = 0.040 gm.
b. 100 c.c. filtered through good filter paper; amount of cholesterin in filtrate = 0.044 gm.
c. 100 c.c. frozen two weeks and filtered; filtrate thoroughly washed amount of cholesterin = 0.042 gm.
d. 100 c.c. inoculated with culture of human colon bacillus and incubated two weeks; cholesterin in bile = 0.036 gm.

Similar observations on normal bile filtered and unfiltered gave comparable results to (a) and (b).

100 c.c. of normal pigs' bile inoculated with culture of human colon bacillus and contaminated with an unrecognized putrefactive organism, was incubated for two weeks. No bile became putrid. Amount of cholesterin after putrefaction = 0.0365 gm.
This represents a loss of 0.0205 gm. during putrefaction (based on comparison with control).

The following observations relate to the influence of acid on the solubility of cholesterin.

Two portions of fresh pigs' bile were taken.
a. 100 c.c.; amount of cholesterin 0.0883 gm.
b. 100 c.c. 3 c.c. normal HCl solution. Allowed to stand 4 days at room temperature. Filtered and residue thoroughly washed. Amount of cholesterin = 0.0781 gm.
(Difference = 0.0102 gm.)

[1] The following observations on the calcium of the blood and the cystic bile from the same dogs are not without interest.

Dog I.	CaO of bile 0.078%	CaO of total blood 0.0153
Dog II.	CaO of bile 0.068%	CaO of total blood 0.0116
Dog III.	CaO of bile 0.056%	CaO of total blood 0.0091
Dog IV.	CaO of bile 0.068%	CaO of blood serum 0.0091
Dog V.	CaO of bile 0.068%	CaO of blood serum 0.014
Dog VI.	CaO of bile 0.056%	CaO of blood serum 0.017

[2] In every instance where calcium is referred to in quantitative terms calcium oxide is meant.

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materially from that of canine cystic bile and is commonly below 0.10 per cent. Why the percentage of calcium in the bile is higher than that of the blood, and higher even than that of the serum, is not yet clear. It appears improbable that the difference is due to the absorption of water from the gall bladder and it is more likely to be dependent on an actual addition of calcium to the cystic bile. This point could be settled by a comparison of the calcium of the blood serum with that of the hepatic and cystic bile in the same patient or experimental animal, but the necessary observations appear to be wanting.

A noteworthy thing about the cystic biliary calcium in pathological conditions is that it seldom varies greatly in percentage from that of normal bile. In this respect the calcium of the bile stands in marked contrast to the cholesterin. The comparative uniformity of the calcium values is observable both in experimental and human pathological conditions. Thus in the experimental inflammations of the gall bladder, already referred to, the average calcium content of the bile was not greater than the average of the normal biles. This applies to the experiments with bichloride of mercury and to those with carbolic acid and ricin. (See Table I.) Increased cholesterin, however, is a feature of these experiments and has been commented upon already. This independence of the calcium and cholesterin of the bile is of interest when we consider the varying composition of gallstones in respect to these constituents.

A moderate increase in the percentage of biliary calcium, or at least high values for calcium—was observed in some of the cases of experimental cholecystitis. The highest percentage observed in any case relates to one of the mercury experiments where the calcium reached 0.166 per cent. In the cases where the calcium appeared to be high no explanation of the fact has been evident. The calcium content of the blood in such cases was not ascertained.

In human pathological conditions, also, the calcium of the bile seldom shows any remarkable increase above the normal. The average calcium in Dr. Baldwin's 40 observations was 0.072 per cent. Three times only was the calcium in excess of 0.120 per cent. Once it reached 0.272 per cent., once 0.214 per cent. and once 0.181 per cent. The solids in these instances were exceptionally high (17.7 per cent., 21.5 per cent. and 21.7 per cent.) but there is no close relationship between calcium and solids in the forty observations regarded as a group. Neither is there any relation between the cholesterin content of these human cystic biles and their choles-

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terin. High cholesterins with low calcium are very common. High calcium with low cholesterin is less common but is sometimes a striking feature. Thus in a case of lobar pneumonia in which the calcium value was 0.272 per cent. the cholesterin was only 0.136 per cent. In seven cases in which the calcium was in excess of 0.10 per cent. advanced chronic nephritis was present in four instances.

It should also be mentioned that in two cases in which the gall bladder contained pigment stones the calcium content of the bile was low, in one case 0.046 per cent., in the second 0.018 per cent. These observations suggest that a high percentage of calcium is not a prerequisite for pigment stone production, although there is no proof that the calcium of the bile was normal at the time when the stones were in process of formation.

What is the source of the biliary calcium in those cases where this element is present in excess? A satisfactory reply to this question cannot at present be given but there are several considerations which give at least a clue to the answer. The very high calcium percentage in the bile, as compared with the normal calcium percentage of the blood serum, in some pathological conditions, makes it unlikely that the excess of calcium comes directly from the blood into the hepatic bile. The widely held view that persons living in limestone districts are especially liable to gallstones led Jankau[1] to feed a dog large doses of calcium phosphate, neutral calcium phosphate and calcium lactate in order to determine whether the biliary calcium could be thereby increased. He obtained negative results. This experiment cannot, however, be regarded as establishing the doctrine that the calcium of the food (and hence of the blood) under no circumstances influences the biliary calcium. An increase in the calcium of the blood may be followed by a moderate increase in the calcium of the bile, for Dr. Wakeman found the average calcium content of the cystic bile of twenty normal dogs to be equal to 0.077 per cent. of calcium oxide, whereas in the biles from twelve dogs intravenously infused with a calcium chloride solution[2] the average percentage was 0.886 per cent., and in one instance reached 0.152 per cent., which is distinctly higher than any normal observed. Although the experimental conditions were unlike any that arise in man, these observations leave it an open question whether the calcium of the bile may not be somewhat increased if for any reason the calcium content of the

[1] Naunyn, Klinik der Cholelithias, p. 15, 1892.

[2] From 1–2 grams of calcium chloride were introduced in this way.

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blood is heightened. But it appears improbable that a considerable excess of calcium can be accounted for in that way, and it is furthermore unlikely that concentration of the cystic bile is an important factor, even where the effects of concentration are added to those of a high calcium percentage in the blood.

The view expressed by Gilbert that the biliary calcium is largely derived from the mucous membrane of the gall bladder through its mucus and desquamated epithelium is probably in large part correct. The acid mucin is probably combined with calcium when it passes the mucus from the mucus glands into the cystic bile or into the hepatic bile. One would therefore anticipate that whenever there arises a catarrhal inflammation of the gall bladder the conditions would become favorable for an increase in cystic calcium and hence for a precipitation of calcium salts. But so far as I am aware careful experimental data relating to this point are lacking.[1]

An excessive concentration of the biliary calcium is probably answerable for the deposition of salts of lime, especially calcium carbonate and calcium phosphate. Calculi containing such salts in abundance are sometimes found in cattle, and foreign bodies in the human gall bladder may undergo incrustation with calcium salts. In true human gallstones, however, the inorganic combinations of calcium are of less significance than the unstable and comparatively unstudied organic compound known as bilirubin-calcium.[2]

The conditions under which bilirubin-calcium separate from the human bile to enter into the composition of calculi are only imperfectly understood and deserve painstaking study, since bilirubin-calcium is so common a constituent of gallstones. Naunyn showed that mere concentration of the bile, at least in the case of dogs' bile, does not suffice to bring about the separation of bilirubin-calcium. Observations already referred to in this paper render it improbable that increased concentration of calcium salts necessarily occasion precipitation. If other conditions are operative, separation may occur when the calcium content of the bile is not excessive. This inference seems to be justified by the fact that one may discover

[1] This point can probably be settled experimentally by means of poisoning by toluylendiamine since this substance markedly increases the mucus of the bile, even in the small hepatic ducts.

[2] Bilirubin calcium can be precipitated by the addition of calcium chloride to an ammoniacal bilirubin solution. It forms a rust-colored flocculent deposit which has a metallic green luster when dried over sulphuric acid. It is a definite compound, in which bilirubin behaves like a monobasic acid, and is represented by the formula $(O_{16}H_{17}N_2O_3)_2Ca$. It is insoluble in water, alcohol, chloroform and ether. A corresponding sodium compound can be prepared.

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bilirubin-calcium in the sediment of human bile in the absence of an unusual percentage of lime. An important factor in favoring precipitation is the reaction of the bile. A pronounced alkaline reaction to litmus facilitates separation. Still we do not know how frequently this factor comes into play in the production of human biliary calculi. Finally, it is known that the presence of proteids may exert a powerful effect in determining a deposition of bilirubin-calcium from the bile. Variations in the biliary proteids may thus come to assume importance for the pathogenesis of calculi. It belongs to future investigations, however, to establish the conditions under which the proteids of the bile play a part in causing the precipitation of bilirubin-calcium. It seems not improbable that this precipitation will be shown to depend on the coöperation of several variable influences, the efficacy of a single factor, such as alkalinity, being commonly dependent on associated conditions.[1]

Relation of Bacteria to Gallstone Production.

It has been shown that the chief constituents of gallstones, cholesterin and bilirubin-calcium, have their origin in local alterations of the mucous membrane of the gall bladder involving desquamation of epithelium on the one hand, and probably an increased production of mucus by the mucous glands, on the other. Hence it is appropriate to inquire into the causes of these local alterations, which are the common accompaniments of cholecystitis.

Bacterial Origin of Cholecystitis.

Modern studies make it clear that the various forms of cholecystitis are in almost all instances of bacterial origin. The chief inciters of the inflammatory process are *B. coli communis, staphylococcus albus, staphylococcus aureus, streptococcus pyogenes,* and *B. typhosus.* Frequently one type of organism is obtained in pure culture from the bile, but at times two or more varieties are found in association. The character of the alterations in the walls of the gall bladder and in the bile depend on the nature of the organisms and their degree of virulence. The chemical characters of the bile, as influenced by these different conditions, have not yet received the attention they deserve. Some characteristic relations have, however,

[1] It is said that the presence of bile salts tends to prevent the combination of bilirubin and calcium (Brockbank). Another factor which may influence precipitation is the quantity of bilirubin in the bile. It is especially desirable that the influence of mucin and of albuminous inflammatory exudates should be studied.

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been noted, which are worthy of mention. Thus the cystic bile in the typhoid infection of the gall bladder, so commonly found in typhoid fever, is increased in amount, watery, dirty brown in color, and contains an abundance of epithelial cells and epithelial detritus. A mild cholecystitis is present in such cases although it commonly happens that there are no distinct symptoms referable to the gall bladder. The occurrence of so much desquamated epithelium is suggestive of a rich source of cholesterin, and it would be well worth while to actually determine the cholesterin in a series of such typhoid biles.

The relation of cholecystitis to gallstone formation is strikingly shown by a table of thirty-two cases of typhoidal cholecystitis compiled by Ehret and Stolz,[1] which were either subjected to autopsy or came to operation. In twenty of these thirty-two cases gallstones were present. This is of course a very high proportion as compared with the percentage observed in autopsies made at random on persons of the same age and sex.[2]

From what we know at present of infectious cholecystitis it is safe to say that such processes afford conditions favorable to the production of cholesterin and mucous in excess, although we do not yet know under precisely what conditions their overproduction is most likely to happen. It seems probable from experimental data that infections of a moderate or slight degree of virulence are most likely to result in conditions favorable to gallstone production, a supposition which accords well with the frequent absence of a history of acute cholecystitis preceding symptoms of gallstone colic.

Occurrence of Bacteria in Gallstones.

It has now come to be generally admitted that a large proportion of gallstones from the human subject contain bacteria in their centers, sometimes living, sometimes uncultivable. M. Galippe[3] apparently deserves the credit of initiating the investigations which have led to this important conclusion. In 1890, about four years after the publication of Galippe's first paper, Welch found the bacillus coli communis and the staphylococcus pyogenes in gallstones, and

[1] Experimentalle Beitrage zur Lehre von der Cholelithiasis, Mitt. aus der grenzgeb. der Med. u. Chirurg., Bd. VII, 2 and 3 Heft, s. 372.

[2] It is noticeable that the average age of these patients with typhoid cholecystitis is less than 28 years.

[3] Galippe's very suggestive paper is entitled Mode de Formation du Tartre et des Calculs Salivaires: Considérations sur la Production des Calculs en général; Presence des Microbes ou de leur germes dans les Concretions (Journal des Connaissances Médicale, 25 Mars, 1886).

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since that time the subject has been studied by Gilbert and Dominici,[1] Gilbert and Fournier,[2] Wandt,[3] Létienne[4] and others. The bacillus coli communis and the typhoid bacillus have been the organism most frequently found.[5]

No careful and extended studies have yet been made with a view to determining whether there is apt to be a relationship between the nature of the bacteria derived from gallstones and the chemical constitution of the stones. There is some reason to think that pure cholesterin stones are often associated with a nucleus which contains colon bacilli, and it has been claimed that the streptococcus pyogenes is apt to be associated with stones rich in calcium salts.

Experimental Production of Gallstones.

The mere presence of pathogenic bacteria in the centers of gallstones, though a fact of much interest, is far from being a proof of the micro-organic origin of the biliary calculi. If, however, it could be shown that the experimental introduction of such bacteria into the gall bladder, under suitable conditions, is often followed by the formation of gallstones hardly distinguishable from human calculi as regards constitution and bacterial contents, this would constitute an indestructible prop to the doctrine that bacterial infections lead to the production of calculi. Efforts to induce gallstone formation in this manner were for a long time unrewarded by success. In 1897, however, both Gilbert[6] and Fournier and Mignot[7] reached the import-

[1] La Lithiase biliare est-elle de nature microbienne? (Soc. de Biol., 16 Juin., 1894.)

[2] Du rôle des microbes dans la genèse les Calculs biliares (Soc. de Biol., 8 février, 1896).

[3] La Fièvre typhoide et lithiase biliare (Bull. Méd., 22 janvier, 1896).

[4] Calculs pariétaux de la vasicule biliare (Congres de Médicine tenu a Bordeaux, août, 1895, et Médicine Moderne, 17 août, 1893).

[5] Only intact calculi should be bacteriologically studied, as the lightest abrasion permits the entry of intestinal bacteria. Calculi covered with a pigmentary stratum are impervious to bacteria, but pure cholesterin stones, without such protection, are liable to permit the invasion of intestinal bacteria after death.

[6] GILBERT, A. Note pour servir a l'histoire de la theorie microbienne de la lithiase biliare, Archives Generales de Medicine, vol. II, p. 257, Septembre, 1898. Gilbert was put on the path leading to success through observing in conjunction with Dominici (Angiocholite et cholecystite typhique experimental, Comptes rendus de la Soc. de Biologie, 23 Decembre, 1893, p. 1033) in 1893, that little concretions ("petites concretions verdatres") formed in the gall bladder of a rabbit with typhoidal cholecystitis. After this methodical attempts were made to obtain more typical concretions.

[7] Reported at the Societe de Chirurgie, May 19, 1897. See Hartmann, M. H., Pathogenie de la Lithiase, La Presse Medicale, No. 19, 2 Mars, 1898, p. 111.

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ant goal for which they had striven, and obtained definite calculi by infecting the gall bladder with the *bacillus coli communis.*[1] It was soon afterwards shown that true biliary calculi very closely resembling those found in human gall bladders, as regards form, color, stratification and bacterial contents, can be experimentally induced through infection with *B. typhosus.*

This result is of the first importance to gallstone pathology, for it has brought a knowledge of the leading conditions requisite for the production of calculi through infection.

The Conditions of Calculus Production from Infection.

(a) *Degree of Virulence of Micro-organisms.*

The mere introduction of virulent micro-organisms into the gall bladder of an experimental animal does not usually suffice to induce gallstone formation. Such organisms generally set up an acute cholecystitis, and the very severity of the process defeats the desired end by causing destructive or atrophic alterations in the mucous membrane of the gall bladder, that lead to interferences with the continued overproduction of cholesterin underlying calculus formation.

If, however, the infective agent be first attenuated in virulence, as suggested and practiced by Mignot, the chance of inducing stone formation is very greatly increased. This is apparently for the reason that bacteria attenuated in virulence set up a subacute cholecystitis peculiarly favorable to the establishment of cholelithiasis. A further precaution which helps to insure success in causing experimental cholelithiasis is the cultivation of the bacteria employed in diluted bile, during several weeks before their introduction into the gall bladder. This procedure appears to facilitate the adaptation of the bacteria to the normal bile, by which they become likely to secure a permanent foothold in the gall bladder.

As to the kind of organisms capable of inducing gallstones Mignot's work shows that *B. coli, B. typhi, staphylococcus pyogenes, streptococcus pyogenes* and even *B. subtilis* may each be successfully employed as inciters of gallstones. But the degree of virulence appears much more significant in this connection than the variety of micro-organism.

[1] The priority in this work belongs to Gilbert although Mignot make the first public announcement of his results. See Cushing, Johns Hopkins Hospital Bulletin (Nos. 101–102), p. 168, 1899. Cushing, Richardson and Lartigau in this country have each succeeded in producing calculi by infecting the gall bladder.

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(b) *Retention of Micro-organisms in the Gall Bladder.*

It is obvious that an essential condition for experimental gallstone production is the retention of the living infective agents within the gall-bladder. Two natural defenses of the normal organism are constantly opposed to the establishment of bacteria in the gall-bladder. One of these depends on the fact that the bile (at least in the case of dogs) is a poor medium for the multiplication of certain kinds of bacteria, and when fresh is not in general an ideal basis for bacterial growth. While it is very doubtful whether even quite fresh bile has any antiseptic action, the relatively slow multiplication of intestinal bacteria in this medium (as compared, for instance, with bouillon) during the first hours after infection, must operate as a protection against injury from micro-organisms, provided the bile has a free exit and is not permitted to remain many hours in stagnation. In health there is a free exit both for the cystic and the hepatic bile, and the normal bile current into the duodenum is such as to constitute a most effective defense against the domicile of bacteria within the bile passages. It is easy to satisfy oneself of the importance of this normal bile outflow by injecting bacteria of moderate virulence into the gall-bladder, where they fail to gain a foothold. The outcome is, however, greatly altered if one first ties the cystic duct or detains the micro-organisms by means of foreign bodies to which they cling. Mignot made effective use of the latter method. In one set of observations these foreign bodies, impregnated with the bacteria to be tested, were permitted to sojourn in the gall-bladder during the entire period covered by the experiments. In another series the foreign bodies were removed by operation after a lapse of three or four weeks, during which time the bodies were operative in keeping bacteria in contact with the mucosa, thus facilitating the establishment of a cholecystitis. In both sets of observations the animals were killed after four or five months and the gall-bladders were found to contain concretions comparable with human calculi, chemically, physically and bacteriologically. Some of the stones resembled the pure cholesterin stones of man. A few contained some sodium chloride and some bile acids and bile pigments.

The Influence of Foreign Bodies.

The observation that various foreign bodies[1] have occurred in the centers of human gallstones has led some writers to attach consider-

[1] Among the bodies noticed have been silk and metal ligatures, globules of mercury, a pin, clots of blood, etc.

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able importance to these accidental inmates of the gall-bladder, as inciters of stone production. If, however, we leave out of consideration the epithelial masses (which cannot be classed as foreign bodies) and the masses of bacteria so often discovered at the centers of gallstones, definite foreign bodies are rare constituents of calculi. Nevertheless, it is interesting to consider for a moment what influence foreign bodies have upon the separation and crystallization of the constituents of calculi. It is certain that sterile glass beads and similar bodies can be left in the gall-bladder of an animal for many months without occasioning the formation of any concretions.[1] This negative result can not, however, be interpreted to mean that foreign bodies are always without influence upon the production of calculi, for it is undeniable that just in so far as they interfere with the complete expulsion of the cystic contents do they favor the accumulation of micro-organisms in the gall-bladder. In this way human gallstones may become operative in facilitating re-infection of the gall-bladder at any time after the death of the bacteria to which they owe their birth. It is interesting that even a stone with a smooth surface facilitates the retention of bacteria in the gall-bladder on account of the layer of fluid which clings to its surface owing to the operation of capillary attraction. Porous stones one would expect to be even more effective owing to their impregnation with bacteria.

The Influence of Mechanical and Chemical Irritants.

Experimental damage to the walls of the gall-bladder by heat (cauterization), scratching, and the application of silver nitrate was found by Myake to be without influence in causing infection. The bile remained sterile in all experiments of this kind. In my laboratory we have had a similar experience with injections of mercuric chloride. These results are of course no evidence that chemical irritants causing an excess of cholesterin in the bile might not in time lead to the production of gallstones even in the absence of infection. On the other hand, there is at present no unimpeachable evidence for the view that stone formation occurs independently of infection, where the stone-forming elements of the bile are increased.

[1] See Ehret and Stolz, also Mignot. A sterile silk thread may in time become encrusted with calcium salts, although the bile remains sterile, but it is doubtful if foreign bodies ever lead to a precipitation of bilirubin or cholesterin.

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The Micro-organisms of Normal Bile.

The not inconsiderable literature relating to the bacteriological examination of the normal bile of dogs, rabbits and guinea pigs indicates that in a majority of instances the bile is sterile—at least so far as can be judged by the ordinary methods of examination, in which small quantities of bile are employed in making cultures. Observations made at my suggestion by Mr. L. F. Rettger[1] are in harmony with this view. Rettger made cultures from the bile from six normal dogs, with negative results in every instance. Smears made with the bile taken from the gall-bladders of thirty-two normal pigs showed growths in only three instances.[2] That the bile of guinea pigs and of rabbits is ordinarily free from pathogenic organisms is made probable by experiments of Fraenkel and Krause,[3] in which they snipped the gall-bladders and permitted the bile to run into the peritoneal cavity without causing infection.

These various results cannot be regarded as absolute proof that the bile is strictly sterile in most instances, for it was found by Ehret and Stolz that the contents of the gall-bladder was infected in almost one-half the animals examined by them. These observers made their cultures with relatively large quantities of bile, thus increasing the chances of discovering bacteria. It may be safely stated, however, that the bile of normal dogs, pigs, rabbits, and guinea pigs commonly is sterile or contains very small numbers of bacteria (usually members of the colon group).

Very similar conditions prevail in the case of human bile studied at autopsy. Although most of the patients examined by Fraenkel and Krause had died either of acute infectious diseases or with tuberculous lesions, the bile was sterile in 105 out of 128 examinations from the same number of patients.

It is notable, however, that although the bile of 34 out of 36 tuberculous patients was sterile by ordinary culture methods, the bile excited tuberculous lesions in 5 of the 11 guinea pigs into which injection of the bile was made. It is thus not unlikely that micro-organisms are present in human bile more often than one might

[1] Zur experimentelle Erzeugung der Gallensteine mit besonderer Berücksichtigung des bakteriellen Verhalten der Gallenwege. Mitt. aus der Grenzgeb. der Med. u. Chirurg., Bd. 6, 4 and 5 Heft, S. 479, 1900.

[2] In one case the colon bacillus, in a second the colon bacillus and an unknown coccus, in the third case one unidentified bacillus, probably a member of the colon group.

[3] Fraenkel and Krause, Zeitschrift für Hygiene, Bd. 32, 1899, p. 77–110.

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suppose from the results of cultures made with small supplies of bile. Even the bile of normal persons may be more often infected than has usually been supposed, but the organisms are probably neither numerous nor virulent in the majority of instances.

Frequency of Human Biliary Infection in Disease.

It is a well established fact that even in the absence of cystic disease bacteria are likely to be present in human bile when there exist pathological conditions in parts remote from the gall-bladder. The *bacillus coli communis* and the staphylococcus are among the most common inhabitants of the bile under these circumstances. Other pyogenic cocci, including the *pneumococcus,* are probably much less often present in the gall-bladder at autopsies made at general hospitals on patients who have not had gall bladder disease.

Some kinds of infective agents are easily missed, on account of the difficulty in making them grow on ordinary media. This is certainly true of the *pneumococcus,* and the experience of Fraenkel and Krause with the *bacillus tuberculosis* makes it likely that this organism is often overlooked. On the other hand, the presence of bacteria in the bile at autopsy is frequently to be regarded rather as the evidence of a terminal infection than as the expression of an earlier invasion.

Biliary Infection in Cholelithiasis.

The presence of bacteria in the bile of cholelithiasis patients is a very common but by no means regular occurrence. W. Peterson[1] in fifty operations for gallstones found bacteria in the bile forty-four times. In thirty-six instances the *bacillus coli* was found, six times this bacillus was associated with the *staphylococcus aureas,* and in four cases the *streptococcus pyogenes* was the companion of the *bacillus coli.*

These figures are probably fairly representative of the cases of cholelithiasis that call for operative interference, although no typhoidal infections happen to occur in Peterson's group of cases. It should be remembered, however, that the character of the gall-bladder infection does not necessarily represent the infective agent concerned with the production of the gallstone, for it may happen that a stone referable to typhoid infection is the means of provoking a cholecystitis due to another organism, long after the original inflammation of the gall bladder has subsided. Sometimes

[1] Brun's Beiträge, Bd. 23.

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the bile is sterile, although stones taken from the same bladder contain living bacteria. On the other hand, a stone from which no organisms can be cultivated is sometimes associated with bile from which bacteria can be grown.

Influence of Human Biliary Stagnation.

It has already been mentioned that an essential condition for the production of experimental cholelithiasis is some degree of impairment of the expulsive power of the gall-bladder. In the absence of such impairment it appears to be extremely difficult for bacteria to gain and maintain a foothold in the healthy gall-bladder. Myake found that ligation of the cystic duct does not lead to infection of the cystic bile, presumably because the unchecked bile flow into the intestine suffices to wash back entering bacteria and to limit their spread.[1] On the other hand, ligation of the ductus choledochus was followed by infection of the cystic bile, because this operation, which lies within the normal bacterial zone,[2] completely stops the bile stream to the duodenum. The results of Ehret and Stolz differ from those of Myake as regards the consequences of ligation of the cystic duct. These observers found that even after the cystic duct had been severed between two ligatures there was a pronounced increase in the number of organisms present in the bile.[3] As these organisms could not have come from the intestine, it is necessary to assume that they arose from the multiplication of bacteria already present in the gall-bladder or possibly that they came from the blood. The eventual death of these organisms appears referable to their feeble powers of adaptation rather than to any increase of the bactericidal action of the bile.

Thus it is likely that while the mere stagnation of the cystic bile may not always be followed by infection of the gall-bladder, such stagnation greatly increases the chance that bacteria will establish themselves in this locality. The information derived from experimentation upon animals makes it extremely probable that whatever causes cystic stagnation in man, increases the opportunity for infection and consequently of cholelithiasis. Among the conditions that

[1] Atrophy of the bladder from ligation of the cystic artery is a result of this operation.

[2] According to Netter and Duclaux, in dogs and rabbits only the lower part of the ductus choledochus (near the papilla) is ordinarily inhabited by bacteria.

[3] It will be recalled that these investigators found bacteria much oftener in the bile of normal animals than have other writers.

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lead to impaired expulsion of the cystic bile are the atrophy of the muscular coat of the gall-bladder and various mechanical agencies which obstruct the biliary passages. The increased liability to gallstone in old age probably depends in a measure on the weakening of the muscular coat of the gall-bladder, but a diminished resistance of the body fluids to infectious agents is possibly another factor. The greater incidence of gallstones in women has been attributed to the mechanical hindrance to the expulsion of bile from the gall-bladder caused by tight lacing. Probably tight lacing acts as such a hindrance, but it fails to explain the considerable liability of the women who do not lace.

It is stated that in fever the gall-bladder is emptied with less completeness than in health, but the evidence in favor of this view is not satisfactory. That the gall-bladder is distended with excessively watery bile in many cases of typhoid fever is well known to pathologists, and it is highly probable that this overdistention is connected with a paretic state of the muscular layer. But it is much more likely that this is a result rather than a cause of infection. Whether fever is in itself a cause of muscular relaxation must be regarded as an open question.

It may, therefore, be said that while experimental evidence makes it highly probable that hindrance to the normal bile-flow from the gall-bladder facilitates infection of the human gall-bladder, our knowledge of the disturbances of cystic function that cause biliary stones is still incomplete.

Mode of Action of Bacteria.

There are two ways in which we may conceive gall bladder infection to operate in the production of gallstones; First by setting up cholecystitis, secondly by causing a decomposition of the bile. Although these processes are probably connected closely, we must consider them individually.

Cholecystitis and its Effects.

One of the consequences of a slight or moderate catarrhal cholecystitis is the proliferation, desquamation and degeneration of epithelial cells. These cells contain cholesterin, a part of which ultimately finds its way into the bile. Probably the quantity of cholesterin increases as time passes, owing to degenerative changes in the cells, the nature of which is obscure. It is well known that pus contains considerable cholesterin and that crystals of chole-

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sterin are more apt to occur in old than in fresh pus. The cause of the increased production is not understood, but is to be sought either in cleavages induced by bacteria or in autolytic decompositions. The same may be said of the cholesterin of epithelial origin. The desquamated epithelium contains some calcium, but whether the calcium of gallstones has this origin or is derived from mucus, is not clear. A careful study of the influence of cholecystitis on the calcium of the bile is a desideratum.

It is noteworthy that in their observations on purulent cholecystitis Ehret and Stolz were unable to find any indications of the presence of cholesterin in the contents of the gall-bladder.

Decomposition of the Bile.

In the course of any infection leading to cholecystitis the bile is liable to undergo decomposition. This is very plainly seen in typhoid fever, in the course of which a large part of the bilirubin is apt to be destroyed. The nature of the decomposition products is unknown and its study would surely lead to results of considerable interest. In purulent cholecystitis, also, the bilirubin disappears, often very rapidly, so that all traces of color may be lost in two or three days. Even in milder types of inflammation, such as commonly lead to cholelithiasis, there is often a decomposition of the bile, the nature of the cleavage products being, however, but imperfectly understood. The presence of bilifuscin and bilicyanin in some gallstones is probably to be regarded as an indication of decomposition of the biliary pigments. It is believed that the bile acids also undergo decomposition at times, with liberation of cholalic acid.

Whether these decompositions are the immediate result of the growth of bacteria in the bile or an indirect effect of altered secretory conditions of the inflamed mucosa is uncertain, but the former origin appears not improbable. Considerable alterations in the composition of the bile may be induced experimentally by modifying normal metabolic processes, but there is as yet no satisfactory evidence that cleavage products arise in this manner.

The decomposition of the bile which is referable directly or more remotely to the activity of bacteria may be presumed to alter profoundly the conditions upon which the presence of certain constituents (cholesterin, lime salts) of gallstones largely depends and may thus have important bearings upon the problem of precipitation. A scientific discussion of this influence is at present not possible.

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Influence of Reaction.

The opinion has already been expressed that variations in the reaction of the bile do not ordinarily play a leading role in determining the precipitation of the constituents of gallstones, but some further discussion of this point will not be amiss.

Very carefully conducted experiments made by Dr. E. K. Dunham* on the influence of the growth of the typhoid organism and the bacillus coli on diluted sterile human bile indicated that even a considerable growth of these organisms after many days occasions only the slightest change in reaction, in the direction of acidity. It is possible that more pronounced acid production would be observed if the period of growth of these organisms had been retarded.†

* Note by Dr. Dunham.

Experiments to determine changes in reaction of nutrient media containing bile were made as follows: Human bile was mixed with five times its volume of distilled water containing 1 per cent. of Witte's pepton and ½ per cent. of table salt, and the mixture filtered. In one experiment, this filtrate was placed in fermentation tubes and sterilized, by the intermittent method, in an Arnold sterilizer. In another experiment the sterilization was accomplished by filtration through a Berkefeld filter. The fermentation tubes were inoculated with the colon bacillus or typhoid bacillus and kept in the incubator at 37° for from 7 to 10 days; blank tubes being kept under the same conditions as controls. After these intervals cultures were made from the fermentation tubes and then their contents titrated with a tenth-normal sodium hydrate solution. In all cases the control tubes were sterile, and the other tubes were shown to contain pure cultures of the bacteria with which they had been inoculated. The appearance of the media in the fermentation tubes and in shakegelatine cultures from them showed that a moderately abundant growth had taken place in the inoculated fermentation tubes.

Five cubic centimeters of the media in the fermentation tubes were diluted with distilled water to 200 c.c., and this diluted solution, which had a light green color, was titrated, phenolphalein being used as an indicator. The amount of decinormal sodium hydrate solution required to effect a distinct, though faint, change of color in the diluted medium was noted, and then the standard alkaline solution added until a drop no longer caused a change of color at the point of introduction. There were no marked differences discovered between the reactions of the media in the control tubes and those in which a growth of the colon bacillus or the typhoid bacillus had extended over a period of 7 to 10 days. The differences noted were not greater than 0.1 c.c. of the decinormal alkali. Such a difference might be due to variations in the amount of evaporation in the different fermentation tubes or to errors in titration owing to the green color of the solution. It appears certain that no alkali is produced, and that, if there is any increase in the acidity of the media, it is very slight.

† Cholesterin is less soluble in an acid than in a neutral or alkaline bile and it is conceivable that even slight changes in the reaction of the bile may

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It has been stated that the presence of free alkali in the bile is favorable to the separation of bilirubin-calcium. We do not know, however, that an alkaline reaction is essential to this separation. An acid reaction would probably be inconsistent with the precipitation of bilirubin-calcium.

Whether the production of alkali (ammonia-amido acids) by the bacteria concerned in the establishment of cholecystitis is really a factor in the precipitation of bilirubin-calcium is still uncertain.

From what has been said it appears conceivable that alterations in the reaction of the bile should exert some influence upon the precipitation of cholesterin and bilirubin-calcium and that changes from an acid to an alkaline reaction or the reverse should have some significance for the stratification, so often observed in gallstones. Nevertheless the variations of some cholelithiasis biles from the normal reactions are probably only very slight and the idea that the constituents of gallstones are precipitated in consequence of alterations in reaction cannot be said to rest on a firm basis.

influence the separation of cholesterin crystals from a supersaturated solution. When cholesterin has once begun to be deposited about the nucleus of a future gallstone it is not difficult to understand why the process continues, until cholesterin is no longer produced in such excess, through the desquamation of cells, that it suffices to keep the bile supersaturated. The real problem is to explain the first crystalline deposit of cholesterin.

It is well known that small masses of altered epithelium and bacteria are commonly found in the centers of cholesterin stones, and it occurs to one that this fact may perhaps be related to the production of acid by the bacteria which often cluster so abundantly about epithelial remains. The multiplication of these organisms with the production of acid might perhaps determine the precipitation of cholesterin at the limited surfaces where the acid is liberated and where owing to the slowness of diffusion the ions might be presumed to exist in greater concentration than elsewhere in the bile. The process of crystalline deposition once begun, the maintenance of an acid reaction at the point of deposit would hardly remain a necessity for further accretion to the young calculus, since according to a well recognized physical law crystalline deposits readily occur where similar crystals already exist.

In the alkaline fermentation of the urine we have a condition which furnishes us with a legitimate analogy. Here, as is well known, we often find deposits of crystalline phosphates in the mucus. But it is in the mucus that the alkali-forming bacteria are growing most energetically, and it cannot be doubted that the early deposition of crystals in the mucus (before their appearance elsewhere and before the entire volume of the urine is distinctly alkaline) depends on the focal liberation of diffusible alkali.

Whether cholesterin is ever precipitated in crystalline form when the bile reacts alkaline to phenolthalein is at present unknown.

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Effect of Concentration.

Mere concentration of canine and human bile appears to have very little influence upon the separation of bilirubin-calcium, so long as bacterial decomposition is excluded. Bilirubin may, however, separate if the concentration be considerable. Mr. Rettger's experiments indicate that dogs' bile is not usually saturated with cholesterin and that some concentration of the bile is possible without occasioning precipitation. The fact that the bile salts are concentrated *pari passu* with the concentration in cholesterin may help to explain the absence of cholesterin separation even after considerable concentration of the bile. Apparently the chief effect of mere concentration of the bile is to increase the liability to separation of bilirubin, but the question has not been fully worked out.

Presence of Proteids.

Steinman found that egg albumin is capable of throwing calcium carbonate out of solutions of calcium salts, and Naunyn showed that this mixture of proteids throws bilirubin-calcium out of solution under certain conditions. Naunyn expresses the opinion that proteid substances may play a considerable role in determining bilirubin-calcium separation from the human bile and thus have much to do with the formation of concretions. During cholecystitis various proteids make their escape from the epithelial cells of the gall bladder into the bile, but we are still in ignorance as to the part they actually play in the production of calculi.[1]

Presence of Foreign Bodies.

Reference has already been made to the comparatively small influence of foreign bodies in causing cholelithiasis. It sometimes happens that the human gall-bladder contains a piece of silk ligature or a bit of metallic suture which has become incrusted with calcium salts. That the action of micro-organisms is not essential to such incrustation is evident from the experiment of Myake in which a silk thread was incrusted with lime salts, although the bile was sterile. Neither bilirubin nor cholesterin could be detected in the incrustation. At the present time there is no evidence that either cholesterin or bilirubin-calcium ever separates merely because of the

[1] Normal canine bile is capable of dissolving considerable quantities of Merck's mucin prepared from bile. May not an increase in the mucin of the human bile have some influence on the separation of bilirubin-calcium?

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presence of a sterile foreign body in the gall-bladder. On the other hand, there is much reason to believe that certain foreign bodies, such as masses of bacteria, and masses of epithelial cells, may act as the nidus for a gallstone in the presence of a bacterial cholecystitis.

Influence of Agglutination.

Harvey Cushing[1] has called attention to the fact that in typhoid fever there may be an active agglutinative serum reaction toward both B. typhosus and the colon bacillus isolated from the gall-bladder. The bile may share the agglutinative properties of the serum. Richardson[2] has examined at autopsy the bile of fatal cases of typhoid fever and found large clumps of bacilli in five out of six cases. It is possible that bacilli agglutinated in large clumps by agglutinations present in the bile are more likely to form the nidus for stone formation than individual unclumped bacilli or smaller clumps of bacilli, but definite information on this point is lacking. It is also uncertain whether a large clump of living bacteria offer a better starting point for the production of a gallstone than an epithelial fragment or cell of equal size. The possibility already mentioned, that living bacteria may influence by their products the reaction of the bile, especially at the seat of their production, and thus facilitate the separation of cholesterin or of bilirubin-calcium, is perhaps worthy of receiving serious consideration in connection with the phenomena of agglutination.[3]

Time Required for Gallstone Formation.

Until within very recent years there was no information as to the time required for the production of a human gallstone. This arose from three circumstances. First, gallstones may lie for an indefinite

[1] Typhoidal Cholecystitis and Cholelithiasis, Report of a case without Previous History of Typhoid Fever, and Discussion of a Possible Agglutinative Reaction in the Bile and its Relation to Stone Formation; Bulletin of the Johns Hopkins Hospital, vol. IX, No. 86, May, 1898.

[2] On the Role of Bacteria in the Formation of Gall-Stones, The Journal of the Boston Society of the Medical Sciences, vol. III, p. 79, Jan., 1899.

[3] The agglutinative properties of the bile have been recently investigated by Arnold Contani, Jr. He finds that the bile of animals immunized against typhoid, colon or influenza bacilli possess a considerable agglutinative activity for these organisms. This activity is, however, distinctly less marked than that possessed by the blood serum. (Ueber die agglutinierende Eigenschaft der Galle; Centralblatt für Bakteriologie, etc., Erste Abtheilung, Bd. XXXIII, No. 9, p. 731, 1903.)

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period in the gall-bladder without causing symptoms. Hence ordinary clinical observations could not furnish the needed light. Secondly, the size, number, consistence and chemical characters of gallstones afford no certain data as to their age. Lastly, no one had succeeded in experimentally inducing true gallstone production. The work of Gilbert and Mignot, already described, has shown that under suitable conditions true gallstones may be experimentally induced in the course of three to six months. We cannot without further information assume that the same period suffices for the production of human stones, but these experimental results are strongly suggestive of the possibility of rapid calculus production in man. An observation made by Hansemann makes it probable that a human gallstone may attain a moderate size in the course of seven months.[1] The case in question is not quite conclusive, because, although the stone was an ordinary mixed cholesterin and bilirubin-calcium calculus, it probably had an extra-cystic origin in the duodenum of a patient who had undergone a gastroenterostomy. The absence of an acid gastric juice was apparently an important element in permitting the production of the stone. Homans[2] has reported an instance in which stone-formation recurred in not more than one year and eight months and Kelve[3] records a case in which the period of re-formation was probably less than a year and a half.

Although positive evidence is still wanting, we are justified in regarding it as probable that gallstones may form in the human gall-bladder in the course of three or four months, when the conditions are especially favorable. Hence when an early operation for cholelithiasis is undertaken the possibility of an early recurrence cannot be left out of mind, as the gall-bladder is liable to be left in an infected state.

Paths by which the Bacteria enter the Gall Bladder.

There are three paths by which micro-organisms may gain access to the liver and through the liver to the contents of the gall-bladder: (1) From bacterial foci which discharge into the general circulation; (2) by the passage of bacteria into the common bile duct from the duodenum; (3) by the passage of bacteria from the intestine into the portal circulation. The first path is probably frequently followed

[1] Ein Beitrag nur Entstehung der Gallensteine, Virchow's Archiv., Bd. 154, Heft 2, p. 380, 1898.

[2] Annals of Surgery, p. 115, 1897.

[3] Die chirurgische Behandlung der Gallensteinkrankheiten, Berlin, 1886.

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by the bacteria that set up the cholecystitis which is responsible for making calculi. The second path at first sight seems the most important and natural one for cystic infection. Yet we do not know under precisely what conditions infection follows this route. In health the duodenum contains few bacteria and these are not of the varieties responsible for the cholecystitis that lead to cholelithiasis. In gastro-duodenitis and duodenitis streptoccocci are sometimes abundant in the duodenum and may perhaps find their way to the gall-bladder. Possibly also in the course of other digestive disturbances colon bacilli find their way along the biliary ducts to the gall-bladder.

There is some reason to believe that the most frequent route for infective agents is the portal circulation. This view has been especially emphasized by Dr. Lartigan[1] of New York, who induced inflammation of the intestine of dogs by means of corrosive sublimate and other irritants. The animals thus prepared were fed bacteria (pathogenic), which were soon found in the bile. In some instances the cystic duct, in others the common duct, was ligated previous to the feeding with bacteria. Hence infection must have occurred through the intestinal mucous membrane, doubtless at the point of injury.

Dissenting voices have been raised against the doctrine that biliary infection occurs through the portal vein. Thus in a recent paper Carmichael[2] states that he injected, in separate experiments, typhoid bacilli, *B. coli communis* and streptococcci into the portal circulation of rabbits without being able to recover bacteria from the bile. He considers that these experiments not only support the view that the liver destroys the micro-organisms that reach it, but render improbable the occurrence of biliary infection by way of the intestine and portal circulation. If, however, we take into consideration the positive results obtained by Blachstein,[3] Fütterer[4] and others, there

[1] N. Y. Acad. Med., Dec., 1902.

[2] The effect of injection of micro-organisms into the portal system, on the sterility of the bile in the gall-bladder: The Journal of Pathology and Bacteriology, vol. VIII, No. III, Sept., 1902, p. 276.

[3] Intravenous inoculation of rabbits with the bacillus coli communis and the bacillus typhi abdominalis: Johns Hopkins Hospital Bulletin, vol. II, p. 121, 1891.

[4] Wie bald gelangen Bacterien, welche in die Portalvene eingedrungen sind, in den grossen Kreislauf, und wann beginnt die anscheidung durch die Leber und die Nieren? Berliner klinische Wochenschrift, Bd. XXXVI, S. 58, Jan. 16, 1899.

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can remain no doubt that the intravenous injection of *B. typhosus* and *B. coli communis* is very often followed by the appearance of the injected organisms in the bile. It is true that in these experiments the bacteria were put into the systemic circulation and may have reached the gall bladder through the cystic artery, without having first traversed the liver, but this appears unlikely. Dr. Welch[1] states his belief that Blachstein's inoculations were very often followed by negative results as regards infection of the bile. These negative results are probably referable mainly to the bactericidal powers of the liver cells. The negative results obtained by Carmichael cannot, therefore, be taken as proof that biliary infection does not arise by way of the portal circulation. A consideration of the evidence at present available makes it extremely probable that the bile may be infected by way of the portal system, despite the bactericidal action of the liver cells. This is true not only of experimental infections in animals, but also of human biliary infection with the organisms of typhoid fever, and the *B. coli communis.* How often infection of the bile arises in consequence of ulcerative lesions in the intestinal tract is not yet clear, but it is certain that such lesions must greatly influence the liability to biliary infection. As yet, however, it is impossible to say with certainty whether the portal system or the direct duodenal path is the more frequent route of biliary infection in man.

Do Gallstones Originate Independently of Infection of the Bile Passages?

The facts that have been reviewed clearly show that through the local action of bacteria upon the walls of the gall-bladder (or bile passages) there may be created all the conditions essential for the production of gallstones. The experimental formation of real calculi makes it safe to conclude that derangements in general metabolism are not essential factors in the process of production. This is, however, no evidence that disturbances of metabolism which modify the composition of the bile, may not under certain conditions play an important part in bringing on cholelithiasis. There are many French and English writers who hold that constitutional states attended with metabolic disorders are a common cause of gallstone formation. It is worth while to examine the foundation on which this view rests.

[1] In a footnote to Blachstein's paper.

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Constitutional Influences modifying the Composition of the Bile.

It is surprising to find how little satisfactory information exists as to the influence of different kinds of dietaries on the composition of the bile. Paton and Balfour[1] found through observations on a woman with a biliary fistula that the amount of solids in the bile rose with the amount of nitrogen excreted by the urine. Brockbank[2] looks on these observations as evidence that more bile salts are produced from a nitrogenous diet than from one poor in nitrogen. Admitting this inference to be sound, one would be led to the conclusion that persons on a diet rich in nitrogen make bile capable of holding in solution more cholesterin than persons who live on meagre nitrogenous rations. Whether there is actually a greater liability to gallstones among those who consume little nitrogen is not conclusively shown by any statistics bearing on this point. I cannot believe that variations in the percentage of bile salts are of great importance in determining the incidence of cholelithiasis, for the reason that the great factor in the formation of cholesterin-containing stones is the local condition of the gall-bladder. In other words, a cholecystitis leads to the local presence of so much cholesterin that the quantity of bile salts in the bile cannot greatly influence the ultimate deposition of cholesterin. There is no reason to think that the percentage of bile-salts in the bile exerts an influence on other biliary constituents than cholesterin.

Whether an increase in the cholesterin of the blood, from constitutional causes, ever markedly modifies the amount of cholesterin in the bile, is a question that cannot now be answered. Fischer[3] reports a case of diabetes with lipaemia and cholesteraemia in which the blood held at least 0.478 per cent. of cholesterin, a quantity greatly above the normal average.[4] The observation is of interest as indicating the possibility of a marked cholesteraemia in a constitutional disease, but there is no certainty that even so great an excess of cholesterin in the blood leads to a significant excess in the cystic bile.

[1] Lab. Reports, Royal Coll. Phys., Edinburgh, 1891.

[2] On Gall-Stones and Cholelithiasis, 1896, pp. 27 and 83.

[3] Über Lipämie und Cholesterämie, so wie über Veränderungen des Pankreas und der Leber bei Diabetes mellitus: Virchow's Archiv., Bd. 172, Heft 1, p. 47, 1903.

[4] Hoppe-Seyler found from 0.2 to 0.6 per cent. of cholesterin in the plasma and serum.

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Further studies of the relationship between the cholesterin of the blood and of the bile are much to be desired.[1]

Influence of Excessive Feeding of Fat.

Gallstones sometimes contain a considerable percentage of fat, which may be present chiefly as a compound of stearic acid.[2] As the origin of this acid is obscure, it was determined to make some observations with a view to learning whether the ingestion of large quantities of fat has any influence on the fat content of the bile, as has been stated by Naunyn. These observations had an unexpected outcome.

Two dogs were fed on boiled beef fat and an extremely small amount of boiled meat. During twelve weeks one dog (weighing about thirty-two pounds) was induced to eat from one-half to one pound of fat daily. During the last two weeks of the experiment he received potatoes mixed with fat. At autopsy the subcutaneous and omental fat was found to be extremely abundant. The liver was very markedly fatty. The bile was normal in quantity, color, consistence and reaction (faintly alkaline to litmus), but contained an abundant sediment of dark brown particles about the size of large grains of sand. These little masses were found to consist of pigmented, highly refractive hyaline material mixed with the débris of degenerating epithelial cells, portions of which were stained readily by osmic acid. No cholesterin could be detected in these particles; certainly none was present in crystalline form.[3]

A second dog (about 19 pounds) was fed for nine weeks in the manner just described. For three weeks he consumed nearly

[1] As red blood cells contain considerable cholesterin, pathological processes attended with excessive haemolysis might be expected to raise the cholesterin of the blood, but I am not aware of any observations bearing on this point.

[2] It is said that gallstones occasionally contain as much as 16 or 17 per cent. of stearic acid. In a series of variegated gallstones examined for me by Mr. Rettger, stearic acid was positively detected in no instance, although in one case it may have been present in very small amount.

[3] Analysis of the bile from this dog gave the following results:

Cholesterin	.360 per cent.
Calcium oxide	.09 per cent.
Ethereal extract, not including soaps, but consisting of neutral fat, cholesterin and lecethin	.97 per cent.
Solids of bile	20.29 per cent.

Although the cholesterin residue was somewhat oily and contributed to give a high weight, it seems clear that the cholesterin in the bile was increased considerably above the normal.

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one-half pound of fat per day. Then for a week he refused to eat. During the last two weeks of the experiment the fat was mixed with potato and was voraciously eaten. The gall bladder contained a little bile of normal consistence, color and reaction (slightly alkaline). Affixed to the base of the gall bladder was a small, black spherical concretion (about 4 mm. in diameter), of somewhat firm consistence. Near it lay numerous small detached irregularly-shaped black masses of apparently the same material. Microscopical examination showed the concretion and the separate masses to consist of deeply pigmented, highly refractive hyaline material. No crystals of cholesterin were detected. The mucosa near the adherent body was considerably thickened and presented numerous small translucent miliary projections.[1] The mucosa for a short distance about the adherent body was covered by a gelatinous layer of great transparency from 1-2 mm. in thickness, apparently consisting of mucinous material.[2]

Sections made through the gall-bladder and the attached intracystic body showed the "concretion" to be made of a group of glands greatly dilated by what is probably an acccumulation of partially transformed mucus, grown firm from inspissation. A fuller description of this body will be given when the results of other fat-feeding experiments are described.

These observations are of some interest on account of their suggestiveness. I have examined the gall-bladders of a large number of meat-fed dogs without having ever observed a sediment like that found in our first dog or an attached body like that discovered in our second. Whatever may be the origin of these pathological conditions, it is improbable that they are dependent on infection of the gall-bladder. Positive evidence on this point is unfortunately wanting, as I carelessly omitted to make cultures from the bile. Nevertheless it seems most likely that the changes observed are of diathetic rather than local origin.

[1] The miliary projections were seen on historical examination to consist of groups of simple glands whose lumina were considerably distended with mucus.

[2] Analysis of the bile from this dog gave the following results:

Ethereal residue after saponifying (including neutral fat, fatty acids, soaps and cholesterin)	3.39 per cent.
Cholesterin found	.213 per cent.
Calcium oxide	.120 per cent.
Solids of bile	22.09 per cent.

Cholesterin figure is somewhat high on account of admixture of oily substance.

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Two leading questions are raised by these experiments; First, do the glandular alterations noted in the gall bladder depend on the pathological conditions of fat metabolism, and secondly, do similar glandular accumulations occur in the human subject and sometimes form the beginnings of true gallstones? An answer to these questions may reasonably be expected from additional experimental observations and from histological studies of the human gall-bladder.[1]

Influence of Gout, Arteriosclerosis and Diabetes.

Some writers have assumed the existence of a close connection between gout and gallstones, and various hypothetical[2] reasons have been advanced to explain the alleged connection. I have been unable to find any substantial evidence in favor of this relationship between cholelithiasis and gout. In the 179 Presbyterian Hospital cases which Dr. Williams has analyzed for me, there is no instance in which a history of gout was noted, although some form of rheumatism existed in twenty of these patients. This showing is thus extremely different from foreign statistics like those of Lenac, where gout was present in 95 out of 166 cases of cholelithiasis. That gout and gallstones should be often associated in countries where both diseases are common is not surprising and the fact does not in itself imply any etiological relationship.

As both arteriosclerosis and gallstone disease increase in frequency with advancing years, we cannot wonder that they should be often observed together in the second half of life. The statistical reports to which I have had access do not certainly establish a special etiological relationship. It is noteworthy that among Dr. Thacher's Presbyterian Hospital cases some form of arteriosclerosis (coronary disease or alterations of the aorta) existed in 80.4 per cent. But in order to give these figures any special significance it would be necessary to show that calculi are distinctly more common in arteriosclerotic persons than in persons of comparable ages dying from all other forms of disease. A study of Dr. Thacher's records from this point of view has been commenced by Dr. Williams, but is at present not completed.

[1] I believe there is much to be learned about the pathology of the bile in its relation to cholelithiasis from systematic chemical and histological studies of the sediments so often found in human gall-bladders (even where autopsies are made early), and from histological studies of the mucosa of the dependent parts.

[2] See Brockbank, *loc. cit.*, p. 85.

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It has been often claimed that there is a close connection between diabetes and biliary calculi, but a critical examination of the evidence does not sustain this contention. On the contrary, it appears to me that gallstones and diabetes are but rarely associated. Dr. Williamson says that Kundrat observed cholelithiasis only once in 92 autopsies on diabetic patients. Of Dr. Thacher's 179 cases two died of diabetes.

The fact that gallstones and diabetes are not more frequently associated has one important bearing on the theory of gallstone formation. Bouchard, who has been a strong advocate of the constitutional hypothesis of cholelithiasis, attributed the alleged relationship between the two diseases to the well known acid production of diabetes. He also believed that pathological acid production in other conditions than diabetes is a factor in causing gallstone formation. If an acid intoxication ever exerts an influence on gallstone formation, it should certainly make itself felt in diabetes, where very large quantities of pathological acids are often produced. Yet there is no reliable statistical evidence of this supposed effect; and it must be said that one would hardly expect the acid intoxication of diabetes to influence the reaction of the bile, as the pathological acid in the blood is so promptly neutralized by ammonia and other bases. There is thus no reason for supposing that free acid ever reaches the bile from the blood. This fact has not been sufficiently considered by those who favor the doctrine that acid intoxications have an influence on gallstone production.

It is plain from what has been said that there is at present no unequivocal evidence that gallstones arise from constitutional derangements unconnected with micro-organic invasions of the gallbladder. On the other hand, it is certain that the cholesterin of the bile can be considerably increased by local irritants unconnected with infection, and it is likely that the requisite local conditions for such increase sometimes arise through purely metabolic disorders. While gallstones are commonly the result of local infections, we should carefully guard against the conclusion that they can never have a diathetic origin. It is at least highly probable that diathetic conditions are capable of so altering the composition of the bile as to materially favor the production of calculi in the presence of suitable local bacterial activities.

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Medical Treatment of Gallstones.

Few facts have as yet emerged from the nebulous region of gallstone therapeutics. We have learned that the surgeon is far more successful than the physician in the treatment of established cholelithiasis. We have learned also that certainly most of the drugs to which cholagogue virtues were once attributed are really undeserving of confidence. The salts of the bile acids and possibly the salicylates possess cholagogue properties, but whether these can be turned to account to bring about the solution of a gallstone must be considered very doubtful. It is certain that through the free use of fat in the dietary the percentage of fat in the bile may be increased above the average, but we do not know whether the increase is ever so great as to cause a marked solvent action on the cholesterin of the gallstones. Such an action appears to me improbable. Other constituents than cholesterin are insoluble in fat. The experimental results which we have obtained from prolonged feeding of fat raise the question whether it is really wise to give patients a rich oleaginous diet, especially in those instances where there is obesity and an inactive habit of life. Restriction both in fats and carbohydrates seems the more rational course and with this there should be free muscular exertion when this is practicable.

It seems probable that in future physicians who treat patients with gallstones will direct their attention largely to measures designed to favor the subsidence of cholecystitis. How much it is possible to influence such a condition we cannot positively say. Hygienic influences that raise the general bactericidal powers of the cells presumably have a beneficial effect upon cholecystitis of infective origin. The value of antiseptics is a matter which future studies will have to decide, but it is not unreasonable to hope that some bactericidal effects will be shown to result from the use of certain antiseptics, which like benzoic acid may enter the bile.

Statistical Note.

Dr. John S. Thacher, of the Presbyterian Hospital, was so kind as to place at my disposal the records of autopsies made there, and Dr. Lindsay Williams undertook to analyze these records with reference to their bearing on the incidence and etiology of gallstones. Some of the results of Dr. Williams' analysis are of sufficient interest to incorporate in this report on the etiology of biliary calculi.

Among 2,371 autopsies gallstones were found in the gall-bladder 179 times (7.6 per cent.). Of these gallstone subjects 99 were

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females, 80 were males. But as the percentage of males among the entire number of patients subjected to autopsy was 65.5, the incidence of cholelithiasis was really a little more than twice as great in females as in males. The distribution of the cases as regards age was as follows:

Males.		Females.	
10 years	1	20–30 years	7
10–20 years	0	30–40 years	19
20–30 years	3	40–50 years	19
30–40 years	3	50–60 years	20
40–50 years	15	Over 60 years	23
50–60 years	25	Unknown years	11
Over 60 years	29		99
Unknown years	4		
	80		

Of 50 women about whom the facts were ascertainable, 70 per cent. had borne children. The adipose was described as "fair," "considerable," or "abundant" in 113, as "scant" or "poor" in 59.[1]

No satisfactory information in regard to the chemical character of the gallstones was reached in the majority of instances. In 32 cases the stones were single. In several instances large numbers of calculi were present; once there were somewhat more than 100, once 267, once the number exceeded 1,000. Very frequently there were from 12 to 50 stones in the gall-bladder. Frequently also there were present from 2 to 12 stones.

As to family history there is nothing notable to record, except that a family history of tuberculosis was obtained in twelve instances. As to personal history the following points were noted: Typhoid fever was known to have occurred in five cases, but this, of course, gives no indication as to the number of stones of typhoid origin. Tuberculosis could be detected clinically in seven patients and was several times found at autopsy, when it had not been recognized during life. Syphilis existed in six cases. A history of gallstones or colic or obstructive jaundice was present in only nine cases. In thirty-three cases the use of alcohol was admitted. In twenty cases there was a history of rheumatism in some form. No case of gout was known to exist, nor could a history of lacing be obtained in any case.

In eleven cases no note was made of the condition of the liver. In fifty cases this organ was normal or nearly normal (gross appear-

[1] In some instances the body was described as emaciated.

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ances). In fifty-six cases the liver was congested or nutmeg. In some of these the liver was also fatty or cirrhotic; the liver was markedly fatty in twenty-eight cases, cirrhotic in twenty. All but six of the twenty-eight cases of fatty liver occurred in women, a large proportion of whom were over forty years of age. The preponderance of women with both gallstones and fatty liver over men is therefore about twice as great as the preponderance of women over men in the entire series of cases. New growths were present in the liver in nine cases; abscess existed in six cases.

Of the eighty-seven cases in which suitable data exist as to the condition of the arteries, arteriosclerosis was present in seventy (80.4 per cent. of these eighty-seven cases). In these cases alterations were found either in the coronaries or in the aorta or in both situations.

The total number of deaths referable directly to gallstones or their sequelae was eleven (6.1 per cent.). This low percentage is probably not referable to any considerable extent to the results of operative interference, as many of the cases occurred before the days of highly accurate diagnosis and early operation.

Perhaps the most striking thing about this analysis by Dr. Williams (to whom I am much indebted) is the large proportion of cholelithiasis patients who showed arteriosclerotic changes. It is not yet apparent, however, that this frequent association possesses any special etiological significance, as it is not clear that similar lesions in persons without gallstones are not equally frequent at autopsies on patients of the same age, sex and habits of life. As the point is one of some interest, a statistical comparison is now being made with a view to determining whether the high proportion of arteriosclerotic lesions in gallstone cases has any etiological meaning.

I wish to express my sense of obligation to Dr. A. J. Wakeman and Dr. Helen Baldwin for their essential contributions to this paper, and to Dr. J. S. Thacher and Dr. Lindsay Williams for facts relating to statistical questions. I desire also to thank Dr. J. Edgar Welch for his zeal in obtaining for me the autopsy material on which Dr. Baldwin's analytical work is based.

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THE MEDICAL AND SURGICAL ASPECTS OF THE DISEASES OF THE GALL BLADDER AND BILE DUCTS.

A STUDY OF 584 OPERATIONS UPON THE GALL BLADDER AND BILE PASSAGES, WITH TABULATED REPORT OF 547 OPERATED CASES.

BY WILLIAM J. MAYO, A.M., M.D.,

Surgeon to St. Mary's Hospital, Rochester, Minnesota.

In nature's defense against infection within the abdominal cavity there are three weak situations,—the Fallopian tube, the appendix and the gall bladder. The first to gain an accepted position was the infective lesions of the tube. The ease of diagnosis and the remarkable results of operative interference contributed largely to this result. The appendix, after much discussion, has also reached an assured place in surgery; but the gall bladder has been slow to receive that attention from the medical public which its importance deserves. The patient is usually along in years and often, by reason of degenerative lesions or adipose tissue, a poor subject for operative interference; and, again, death does not frequently come with that tragic suddenness which ofttimes marks appendicitis.

Like the appendix, the gall bladder is a dependent organ with a limited outlet, connected, although less directly, with the intestinal tract; but fortunately at a point in which the micro-organisms normally present are not so active. Both organs are liable to stone formation; but infections of the gall bladder are usually due to less virulent bacteria, and its better blood supply and distensibility equalizes that tension which is so fatal a characteristic of the inflamed appendix. Perforation and sudden death, therefore, are less frequent in diseases of the gall bladder.

As a cause of chronic distress and disability in adult life, however, diseases of the gall bladder nearly equal in frequency those of the appendix, while in later years, the gall bladder undoubtedly takes first place. The inflammatory affections of the Fallopian tubes which gave such an impetus to pelvic and abdominal surgery have dropped to third place with lesions of the stomach a close competitor. In St. Mary's Hospital in 1902 the relative proportion of these operations was:—appendix 345, gall bladder 143, ovaries and tubes 98, stomach 77.

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The 534 operations upon the gall bladder and bile passages which form the basis of the report were performed upon 518 patients with 19 deaths, a mortality of 3.5 per cent.; of the total number 510 were for gallstone disease with a mortality of 3 per cent. Considering stones in the gall bladder as uncomplicated, there were 208 cases with 2 deaths, mortality of less than 1 per cent. On the other hand, grouping complicated, stones in the cystic duct, stones in the common duct, infections with and without stones and malignant disease, there were 326 cases with 16 deaths, a mortality of 5 per cent. This is a most significant fact and offers a strong argument in favor of early operation. It has been said that of the 5 to 10 per cent. of adults who have gallstones, the large majority do not have symptoms. I am convinced that many times we physicians do not recognize and attribute symptoms really present to their proper source in the gall bladder,—we too often make indefinite diagnoses of dyspepsia or indigestion.

The standard of measure in the diagnosis of gallstones is the "colic," yet this is but a small part of the clinical picture and is readily diagnosticated. Not so the chronic distress and stomach disturbance which the evolution of the pathological process so often develops. In the latter case, the victim goes the round of the reputable practitioners of medicine and then, unrelieved, falls into the hands of the charlatan or patent medicine vender, until complications develop or a condition of encapsulation is established, subject to occasional attacks of regional inflammation.

That the large majority of adults with gallstones never suffer is true, yet these stones but "slumber," with the possibility of a painful awakening. Once "active," the chances of permanently regaining a condition of "rest" is not good, although the interval may last for years. Under normal conditions, the bile has been supposed to be sterile; but it has been demonstrated that if collected in sufficiently large quantities, a few bacteria can be detected, and, as shown by Lartigau, it is possible that the necessary attenuation of the infective agents is produced by passage through the liver, and that stagnation of the infected bile in the gall bladder is the usual cause of the "stone building catarrh," rather than an ascending inflammation from the intestines through the ducts. A gall bladder containing stones is always infected, and when this organ once becomes restless from the irritation of its host, the chance of a complete reconciliation is improbable. In 19 cases, we have found and removed unsuspected gallstones during an abdominal

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operation performed for another purpose, and in the light of the findings, an inquiry properly directed demonstrated that the majority of these patients had suffered at times, but that the trouble was attributed to another cause. In some of these cases, marked contraction of the gall bladder or dense adhesions indicated that there had been at one time an active disease present. The truth is that there are varying degrees of gallstone activity, of which the form characterized by "colics" is the most noticeable for obvious reasons. Not only is the mortality in the uncomplicated cases low, but the operation as a rule is of the simplest character,—opening the gall bladder, removal of the stones and attachment of the fundus of the organ to the abdominal wall with temporary drainage of the bile to the surface. Cholecystostomy not only effectually cures the condition, but by permanently elevating the fundus, the cystic duct is brought to the bottom of the cavity and gravity drainage ensues in the future. The "ideal" operation, that is, complete closure of the gall bladder incision, has been successful in many cases of slumbering gallstones accidentally found during the abdominal operation performed for other purpose. This is a dangerous practice in active gallstone disease, as activity means an increased infection. As long as the stones do not become lodged either in the pelvis of the gall bladder (Hartman's pouch), or the cystic duct, the usual short colic is the chief symptom, and cholecystostomy is sufficient. If the stones are impacted in either situation, the colic is replaced by a constant distress less acute but more continuous. The gall bladder becomes distended and its walls infiltrated with inflammatory products. In such cases, as a rule, the stones can be dislodged and brought up and out through the gall bladder, and an ordinary cholecystostomy performed, but occasionally an incision through the wall of the duct is necessary for relief of the impaction, followed by suture of the duct and cholecystostomy or ablation of the organ itself. Operation in 183 cases of stones impacted in the pelvis or in the cystic duct resulted in six deaths, a mortality of 3¼ per cent. This included, however, a number of cases of severe infections. Should the walls of the gall bladder have undergone marked changes, or angulation and stricture of the cystic duct, resulting in mucous fistula, seem a possible outcome, cholecystectomy is more certain to afford permanent relief. If the cystic duct is completely obstructed so that the gall bladder contains no bile, it is a simple operation to detach the organ from the liver and ligate with catgut at the base; but if the gall bladder participates in the

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biliary circulation in spite of the obstruction, it is not always wise to ligate the cystic duct, especially if there is a cholangitis present. Under such circumstances, if it is decided to remove the organ, the cystic duct should be left open for drainage of the bile to the surface. It is in this class of cases that we have, where possible, removed the fundus and the entire mucous membrane; the peritoneum and outer layers of the base of the gall bladder being retained to form a pouch, into which the end of a drainage tube can be securely fastened for the purpose of safely conducting the bile to the surface. In 75 cholecystectomies, either complete or with the modifications outlined, there were but two deaths.

Kehr, Robson, and all of large experience in gallstone surgery, unite in declaring that they have not known gallstones to reform after operation, and this has been our experience. In our early work, it sometimes happened that stones would be discharged from the fistula subsequent to the operation or occasionally the outer opening would cicatrize before all the calculi were discharged, and those retained gave rise to future colics, requiring secondary operations, not because the stones had reformed, but because the primary operation had been incomplete.

It is the fond hope of the patient that the stones will pass down and out through the common duct, and not infrequently this is the case; but there are usually more behind. We have never operated upon a patient who has passed calculi that we have not found more in the gall bladder. The passing of the calculus, instead of being a reason for delay, is an indication for operation, as the next labor may miscarry and lodge the stone in the common duct, in which situation the results of operative interference are no longer certain on account of the attendant jaundice and infection of the common and hepatic ducts.

Surgery of the common duct has become a fairly safe operation, the mortality depending more upon the condition of the patient than any difficulties in the technique. This, of course, has some marked exceptions. To the late Dr. Davis of Alabama we owe the most important contribution to this subject. He both experimentally and clinically called attention to the necessity of freely draining the bile to the surface after common duct operation and demonstrated that suture of the duct was usually unnecessary and occasionally harmful. This saved much time in a class of cases with general debility from jaundice and infections of the ducts, in which time is an element of great value. If the cystic duct is open, enabling the

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bile to readily flow outward through the gall bladder to the surface by means of cholecystostomy, suture of the common duct may be advisable but not otherwise.

To Robson we owe great improvement in the technique of this operation, especially the sand bag under the back at the level of the liver to tilt the costal margin outward on the principle of a reverse Trendelenberg position. The incision of Bevan through the abdominal wall, as modified by Robson, in dispensing with the lower angle and carrying the upper limb close to the costal margin, enables one to draw the liver downward and outward, and straightens the angle of the cystic duct at the common duct. In this way, removal of common duct stones is rendered easy. In many cases the common duct is so dilated by stones impacted in the terminal portion that the finger can be easily introduced, and by aiding the extraction with counter-pressure with the other hand over the duodenum, the stone may be coaxed backward and out of the duct incision. The finger can be used in the same way in the hepatic ducts. In no other way in some cases can one be certain the ducts are free. In a few cases, incision of the duodenum and direct extraction, as advised by McBurney, may be necessary. We had two such cases in our earlier experience. The "ball-valve" stone so graphically described by the late Christian Fenger was met with nine times. Kehr has extended the usefulness of hepatic drainage by direct tubage of the hepatic duct, and has shown us how to cure cases heretofore considered hopeless. Out of the 534 cases we had 58 of stones in the common duct with three deaths, 5⅕ per cent. The relative proportion of common duct cases was 11 per cent. of the whole, considerable less than in either the Kehr or Robson series, who report a percentage of nearly 20 per cent. Even 11 per cent. is too high. Gallstones should, in the large majority of instances, be diagnosticated and sent to the surgeon before common duct symptoms clinch the diagnosis and force operation upon the patient.

Chronic pancreatitis, shown by enlargement of the head of the pancreas, was met with in connection with gallstone disease 18 times. In four of these patients, cholecyst-duodenostomy was performed and all of these cases recovered. In the remaining 12 cases no special treatment beyond the removal of the gallstones and establishment of drainage was adopted. One case of acute pancreatitis and fat necrosis, due to a cholecystitis from one large gallstone in the gall bladder, recovered after operation, as did one subacute hæmorrhagic cyst of the pancreas from the same cause.

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It has been noted experimentally that high grades of infection seldom cause stones, although these infections are most liable to occur in patients who already suffer from calculi. In the acutely infected cases, gangrene or perforation of the gall bladder may happen. In the more chronic infections of this type, the symptoms are almost identical with gallstones. In 534 cases we had 27 of this chronic character with three deaths. The mortality at once demonstrates that the infection was more virulent than in gallstone disease. The deaths were usually from that condition called by Eisendrath "hepatargia," or cessation of liver function, which the experimental work of Adami helps us to appreciate. These cases of chronic cholecystitis are very interesting because of the liability to overlook the condition at operation on account of the absence of gallstones, although the gall bladder shows evidences of trouble.

In the benign series it is to be noted that 16 cases came to secondary operation, 14 were cured by the second operation, 2 required several operations before cure resulted. The average stay in the hospital was slightly less than three weeks; the attempt being to remove all of the stones at the primary operation and make the drainage more efficient by accurate placing and retention with catgut sutures, which are absorbed before it is necessary to remove the drains. This reduces the quantity of packing to a minimum and enables better closure of the wound without marked hernia liability. The sutures closing the abdominal incision are left in place two weeks, which makes it quite safe to allow the patient to get about early, an important factor in the recovery of old people. If the patient is cholemic, we give chloride of calcium as a prophylactic treatment against hæmorrhage. Otherwise we have not found a special preparatory treatment to be of value beyond the ordinary preparation for laparotomy. The after care is very simple. If possible the bile is conducted into a bottle and the drainage packing is not disturbed until the end of the first week, and after removal of the drains, repacking is rarely necessary. In severe cases, bile drainage to the surface is essential and for this purpose the cystic duct, if unobstructed, offers an easy and safe avenue of escape from the hepatic ducts. In few cases have we found direct incision and tubage of the common duct, as recommended by Kehr, advantageous.

Malignant diseases of the gall bladder and bile ducts was met with 24 times, or 4 per cent. of the total number of cases. The proportion was about four times in the gall bladder to once in the

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ducts. In some cases the exact origin could not be determined by a reasonable exploration. Five times the gall bladder was removed for cancer. In two of these cases a considerable portion of the liver was also excised. Three patients are alive, one nearly two years; but, unfortunately, with recent recurrence and obstructive jaundice. In one case a carcinoma involving the terminal end of the common duct was excised by the duodenal route; recurrence after one and one-half years necessitated cholecyst-duodenostomy. As the presence of gallstones occurs in only 15 per cent. of secondary cancers of the gall bladder and in over 80 per cent. of primary cancers, we must conclude that they are the chief etiological factor in the production of malignant disease of this organ. In nearly all of our cases gallstones were present and a clear history of active trouble could be elicited, although there may have been years of quiet between the colics and the development of the cancer. While the possibility of cancer could not be of itself considered an indication for the removal of gallstones, it is worth considering, as about one case in twenty-five coming to the operating table in this series had malignant disease. The usual precancerous condition would seem to be a gall bladder with thickened wall due to chronic infection and calculi. It is just this class of gall bladders which are now being subjected to excision rather than drainage, and it is probable that in the future many cases of cancer will be removed in an early stage with permanent cure.

Palliative operations for malignant disease of the gall bladder and bile ducts are not of great service. In a few cases of common duct obstruction, cholecyst-enterostomy gives relief for a time and if the duodenum can not be easily reached the transverse colon serves as well for the purpose of anastomosis.

In five cholecyst-enterostomies for malignant disease, four were attached to the transverse colon with one death and in one to the duodenum. In non-malignant diseases we attach to the duodenum, if possible, the Murphy button being used in all.

As an appendix to this paper is attached a statistical table which can be studied by those interested in the subject.

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A Table of 547 Operations Upon the Gall Bladder and Bile Passages.[1] Occurring in St. Mary's Hospital of Rochester, Minnesota, from June 24, 1891, to May 13, 1903.

St. Mary's Hospital reports 527, Minnesota State Hospital and Private Practice 20. Service of William J. and Charles H. Mayo.

OPERATIONS FOR BENIGN DISEASE.

	Total.	Recovered.	Died.
Cholecystostomy. Stones in gall bladder, cystic duct or both	299	296	3
Cholecystostomy. Polypus in gall bladder	1	1	
Cholecystostomy. Gall-bladder stone with acute pancreatitis and fat necrosis	1	1	
Cholecystostomy. Cholecystitis with and without stones	51	46	5
Choledochotomy. Stones in common duct	59	56	3
Cholecystectomy. Gallstone disease	56	55	1
Cholecystectomy. Cholecystitis	9	8	1
Cholecystectomy. Cyst of gall bladder containing 10 qts. supposed to be ovarian	1	1	
Cholecystenterostomy. Chronic pancreatitis and jaundice, 4 with gallstones, 1 without	5	5	
Perforation of calculus, abscess and general peritonitis	2		2
Division of adhesions	16	16	
Duodeno-choledochotomy. Stone ampulla of Vater	1	1	
Exploratory. Negative	21	21	
	522	507	15

OPERATIONS FOR MALIGNANT DISEASE.

	Total.	Recovered.	Died.
Cholecystectomy	4	3	1
Cholecystostomy. Obstruction common duct	5	3	2
Cholecystectomy and partial hepatectomy. Cancer of the gall bladder	1	1	
Duodeno-choledochotomy. Cancer ampulla of Vater	1	1	
Cholecystenterostomy. Malignant obstruction of common duct	4	3	1
Exploratory. Inoperable cancer	10		
Malignant, total	25	11	4
May 13, 1903	547	518	19

[1] More than one operation performed at one time, only the major is tabulated.

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THE MEDICAL AND SURGICAL ASPECTS OF THE DISEASES OF THE GALL BLADDER AND BILE DUCTS.

THE SURGICAL TREATMENT OF ACUTE AND CHRONIC OBSTRUCTION OF THE DUCTUS CHOLEDOCHUS, FROM CALCULUS OR TUMOR.

BY PROFESSOR DR. HANS KEHR,

of Halberstadt, Germany.

GENTLEMEN:—The keen-witted German poet Lessing has said: "Seines Fleisses darf sich Jedermann rühmen" (Every one may take pride in his own industry). Scientific men, as a rule, take little advantage of this privilege, leaving the question as to whether their industry has borne fruit and thus proved a blessing, to the judgment of their contemporaries or of posterity. So I will not boast of the industry incident to the performance of some eight hundred laparotomies for gall-stones, but think, nevertheless, that without incurring from you an accusation of immodesty, I may assume that my efforts in behalf of gall-stone surgery have not been altogether in vain, and that my numerous communications pertaining to the much debated ground of cholelithiasis[1] have met with some appreciation in this country. Were this otherwise, gentlemen, you certainly would not have invited me here to report to this assemblage upon the work which I have done.

Grateful as I am to you for the distinction thus accorded me, and highly as I appreciate the honor you have conferred upon me, I cannot, nevertheless, conceal from you that it is with considerable misgivings that I undertake the performance of the task you have given me; because I do not know that I shall be able to tell you much that is new. American surgeons particularly,—and I mention only Keen, Mayo, Morison, Murphy, McBurney,—have done most excellent work; have indeed been pioneers in the field of gall-stone surgery, so that it would have been quite unnecessary to summon me, the surgeon of a small provincial German town, to address you:—from the lips of your own countrymen could you have certainly heard much that was better, much that was more excellent. Inasmuch, however, as it is your wish to hear me at this time, I will make every endeavor to fulfill my office.

[1] The publications from my private clinic to date on the subject of Gall-stone Diseases will be given at the end of this paper.

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As the order of the day, however, is that addresses shall not exceed twenty minutes in length, I am unfortunately prevented from carrying out my original design of reviewing with you the eight hundred operations for gall-stones which I have performed. Such a review could only imperfectly be carried out in a full hour, and I shall accordingly, from the wide field of gall-stone surgery, select but a brief chapter, which is, however, the most important one, namely, "The treatment of acute and chronic obstruction of the ductus choledochus by calculus or tumor."

I would, furthermore, direct your attention to my address delivered in the autumn of last year, at the Naturforscherversammlung, in Carlsbad, entitled: "A review of seven hundred and twenty laparotomies for gall-stones, with particular consideration of ninety cases of drainage of the hepatic duct."[1] Through the kindness of Dr. Stern of Philadelphia, for which I here express my warmest thanks, this address has been translated, and has, I hope, been read by most of you. I am able, therefore, to assume that you are already in a measure familiar with my opinions regarding early operations as well as my views as to the indications for operation; and that you are accurately informed of their immediate and ultimate results.

In that address I discussed briefly the treatment of acute and chronic obstruction of the ductus choledochus, and what I have to bring before you to-day, I beg you regard as an amplification of what has been said there.

We differentiate an acute, and a chronic, obstruction of the ductus choledochus, due to calculus or to tumor.

I will state at the outset that acute obstruction of the common duct by *tumor* plays practically no rôle at all, inasmuch as it almost invariably passes over into the chronic form. Acute obstruction by *calculus,* however, demands particular discussion, because it is, on the whole, not uncommon, frequently disappears entirely, and in but a relatively limited number of cases lays the foundation for chronic obstruction of the duct.

The phenomena of acute obstruction of the ductus choledochus by calculus are so typical, so striking, that it is unnecessary to dwell upon them at length. It would likewise lead too far to investigate in what degree the muscular forces of the entire system of the biliary passages participate in forcing the stone through the ductus chole-

[1] Ein Rückblick auf 720 Gallensteinlaparotomien, unter besonderer Berücksichtigung von 90 Hepaticusdrainagen.

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dochus into the duodenum, and what other agencies collaborate to the same end. Basing my belief upon observations made in numerous autopsical demonstrations in living subjects, I am, for my own part, firmly of the opinion that the pressure of the bile, dammed back by inflammatory processes, is the chief factor in forcing stone through the duct. Not infrequently we have to do with several stones which in the course of an attack of biliary colic, or during the course of many daily renewed attacks, pass into the ductus choledochus. At all events we cannot, at the time of the colic, determine whether the stones are large or small, whether they remain permanently in the ductus choledochus, or whether they pass through. And inasmuch as it is, on the other hand, possible that they may remain behind, thereby becoming latent, i. e., resting there without giving rise to symptoms, and as it is, on the other hand, not impossible that they may all pass through, *the expectant treatment is the only rational one in the presence of acute obstruction of the common bile-duct,* and acute obstruction of the common bile-duct lies in the province of the physician; it is his duty, by means of rest, hot applications, the administration of eunatrol, sodium salicylate, etc., to strive to assist the powers of nature, in bringing about a natural elimination of the stone. On these grounds I do not operate when a patient is sent to me—as often happens—with acute obstruction of the ductus choledochus. I wait quietly for developments, and have the stools carefully examined for the presence of calculi. If stones are found; if the icterus entirely disappears; and if absolutely no tenderness of the hepatic region remains; there is, of course, no ground for an operation. Even in case no stone be found in the fæces, as soon as the icterus is absolutely gone and the colics have ceased, no operation is necessary, because it is possible for the stone to have passed and been disintegrated in the intestines. So that the matter of stones having been passed by stool or not, does not play an absolutely decisive rôle in settling the question of operation.

There are exceptionally, however, cases of acute obstruction of the common bile-duct which behave most obstinately. The icterus does not subside; fever and rigors come on; the appetite becomes less and less, and a positive collapse of the patient's strength is manifest. Even in such cases improvement may suddenly take place through the removal of the obstacle, as, indeed, on the other hand, through cholæmic hæmorrhage into the stomach or the bowel, a fatal termination may be precipitated. I would advise, in such cases, to take

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the matter of operation earnestly into consideration; an operation which, according to the conditions of the case, should consist in draining the hepatic duct with concurrent cystostomy or cystectomy, or which, in extremely enfeebled patients, may consist in a cystostomy alone. This particular indication for operation presents itself but seldom; as in eight hundred operations I have found it necessary to operate for acute obstruction of the ductus choledochus but four times.

There are, however, cases of acute choledochus obstruction due to calculus, which recur every week or two for months and years, and thereby rob the patient of all pleasure in life and incapacitate him from work. In such cases, even though after each attack one or more stones are found in the fæces, so that physician and patient both are ever led on by the hope that at length all the calculi may have been passed, experience teaches us that usually the gall-bladder is occupied by hundreds of stones, and that alongside of the smaller concretions, of a size that might pass through the duct, there still remain others larger whose dimensions make it impossible for them to be evacuated "per vias naturales." Should internal treatment fail to bring about a cure of these frequently recurring acute obstructions of the common bile-duct, surgical treatment is surely in order. In these cases the nature and duration of the colics; the accompanying fever; the addiction to the use of morphine; the age, sex and social standing of the patient; his condition in the intervals, and finally, the skill and experience of the operator will determine the decision. One who has had no considerable experience in gall-stone surgery will perhaps do well rather to play the part of a Fabius Cunctator than to allow himself to be led on by a "furor operativus" to a somewhat difficult operation. It is just in these cases of cholelithiasis which drive the patient almost to desperation that the surgeon experienced in gall-bladder operations is able at one stroke to cut short the colics and to eliminate once for all this burden from his patient's life without exposing him to any considerable danger. In general, however, these forms of acute choledochus obstruction are rare, so that the physician does not often have occasion to consider the necessity of the operation.

In marked contrast to the comparative rarity with which we encounter the indications for operation in acute choledochus obstruction, is the great frequency with which the indications are met in *chronic obstruction of the common bile-duct.*

Here too, of course, we have cases which may come to a favorable

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issue without operation: cases of chronic choledochus obstruction from stone with absolute latency may occur, i. e., the patient has neither icterus, nor colics, nor fever, although calculi as large as a hazelnut or as a walnut may be lying in the ductus choledochus. I have observed this in numerous instances on the living subject, and frequently this latency is taken for a cure, although the condition is actually but one of absence of symptoms. Again, in even desperate cases, a quite unexpected spontaneous cure may occur, in that by pressure ulceration, a choledocho-duodenal fistula may form and the stone pass through, or at least the infected bile escape.

It is not, however, advisable to wait for this natural process of cure, first, because it is very rare, and secondly, because it is associated with dangers even greater than those of operation. Personally, in cases of chronic obstruction of the ductus choledochus, I do not trust to the caprices of a natural cure, but rather to my good, sharp knife; and I maintain that although in a certain percentage of cases a spontaneous cure may occur by waiting, the dangers of this expectant plan are far greater than those of surgical interference. Personally in the last two years I have lost scarcely three per cent. of operative cases of chronic choledochus obstruction that were not complicated with purulent cholangitis, sepsis or carcinoma; and though I know that these favorable results are due to the great practice and experience which have incidentally been mine, an operative mortality of even twenty per cent. should not be deemed excessive when one calls to mind the fact that of patients suffering from chronic obstruction of the ductus choledochus with fever, rigors, and ever-recurring icterus, eighty per cent. surely succumb sooner or later to the disease. One who is acquainted with the dangers of this disease certainly is in error when he advises against operation.

Just as the useless waiting by physician and patient for the formation of a choledocho-duodenal fistula so often leads to the general infection of the biliary system with its most disastrous results, so, likewise, has the favorable effect of a sojourn in Carlsbad upon chronic obstruction of the common bile-duct been a powerful drawback to the development of the operative treatment. There is no possible doubt that at Carlsbad the manifestations of chronic choledochus obstruction may entirely disappear, the icterus cease, the appetite return, the fever subside, the colics become more infrequent: but the calculus is neither dissolved nor flushed out, but remains quiescent where it is, the accompanying cholangitis subsiding through the administration of the alkaline-saline waters. I have observed

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this in nearly all the patients upon whom I have operated for chronic choledochus obstruction; they had almost all of them been previously to Carlsbad. No one can convince me that a cure of cholelithiasis, that is a washing out of all the calculi, occurs any oftener in Carlsbad than elsewhere. What is achieved there is merely the induction of the cholelithiasis into the condition of latency. If this latency be maintained, it is well to wait before operating until it is interrupted by a fresh outbreak of colics, etc.

If, gentlemen, you have read attentively the address delivered in Carlsbad above referred to, you will have learned that with many forms of cholelithiasis, particularly in chronic relapsing cholecystitis, I am content with its induction into the condition of latency, and neither demand an early operation nor, indeed, when a course of treatment at Carlsbad has begun to show good effects, do I insist upon surgical measures. You will have learned, also, that I exact very strict indications for operation, and that I do not belong to those surgeons who are "ever ready to cut." Even in chronic choledochus obstruction, I demand operation only when no tendency to complete latency is manifest, and when renewed troubles continually assert themselves. But, if we expect to accomplish anything by an operation, it will not do to postpone it too long. It is greatly to be regretted that patients with chronic obstruction of the common bile-duct present themselves relatively so seldom at the proper time for operation, and the statement which I have previously made is still true to-day: namely, that "for the very reason that it is temporarily effective, a course of treatment at Carlsbad is often, in the long run, harmful, and the drinking of 'Sprudelwasser' in chronic choledochus obstruction more dangerous than opening the belly." For the momentary improvement holds the patient back from consulting the dreaded surgeon; he waits for a second attack of colic; a third attack comes on; here, too, the waters develop their wonderful potency; in a fourth attack they fail; and in a fifth attack there occurs a severe infection which, in brief time, carries off the patient, or brings him into the hands of the surgeon, who now operates, finds a severe cholangitis, loses his patient and is blamed for the unfortunate outcome, while in truth, in most cases, the responsibility should rather lie upon the too long-continued internal treatment.

In these latter years conditions with us in Germany have measurably improved, since the successful results of the surgical treatment of cholelithiasis have become more and more widely known to

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the general public; nevertheless, many patients still die whose rescue by the scalpel would not be a difficult task.

Positively, therefore, gentlemen, as I would urge upon you the operative treatment of chronic choledochus obstruction, yet I am well aware that in a given case it is not easy to determine the right moment for operation. The operation is done to the best advantage during the free interval, when fever, icterus and colics are absent, but I have also operated with good results during acute exacerbations of the obstruction. The operation, however, is absolutely contraindicated when the cholangitis is very extensive, and complicating diseased processes, which of themselves contraindicate anæsthesia, are present in the kidneys and lungs. Not infrequently the disease proceeds in acute and violent exacerbations of a hitherto moderate cholangitis, with such prostration of the powers of the heart that, with the best intention of all concerned, no reasonable opportunity for surgical intervention presents itself. There are also cases, and I see them, alas, frequently, in which, for the time being, operation is more dangerous than waiting, and in which I myself have to warn those interested to have patience. In such cases there is always surprise that I, the reputed eager operator, am so reluctant. For both the patient and the attending physician, even those not otherwise ready to invoke the surgeon's aid, ardently desire the operation, and it is purely on the ground of experience that I have to dissuade them from the operation as useless, as I am convinced that the expectant treatment gives better results than the operative. It is very difficult in these cases to decide upon the proper course, and only a large experience will enable one to do so. That surgeon only, who with keen insight recognizes the condition of the whole system, who does not, as so frequently happens in his interest in his specialty, forget that the operation does violence to the heart, the lungs and the kidneys as well as to the liver, the gall-bladder and the ductus choledochus,—in a word, that surgeon only, who is at the same time a good physician,—will be able, in such cases, to hit upon the right course.

It is especially foreign to my intention to represent the operation in chronic obstruction of the common bile-duct as easy, without danger and simple of execution. It is impossible to perform choledochotomy without general anæsthesia. Ether, as well as chloroform, is a dangerous agent, and the possibility that now and then a patient will succumb to the deleterious effects of the anæsthetic upon the liver, kidneys, heart or lungs cannot be excluded. Against hæm-

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atemesis, peculiarly prone to occur in cholæmia; against thrombosis and embolism, no patient can be absolutely insured. Ventral hernia and adhesions, with their distressing and often even dangerous complications, may occur after an operation for gall-stones, and there is, moreover, the ever-present danger of relapse, which, especially with an ill-advised technique, i. e., with suturing of the ductus choledochus, is no uncommon sequel to the operation.

However, all these possibilities occur with such relative infrequency that the immense benefit attending surgical interference is, on the whole, but very little curtailed; and, as offset against the expectant plan of treatment with its own attendant dangers, the operative procedure still remains as that lesser evil to which each of us gladly has recourse when no other choice is left.

Weighing however carefully I may, the chances between waiting and operating, I am always forced finally to recommend operation, and am convinced that thereby I have saved many from inexpressible sufferings and certain death. It is true many factors affect the problem of bringing a majority of cases to a successful termination—irreproachable asepsis, great practice and experience, complete mastery of the technique, rapid and precise operating, attentive and careful after-treatment—should the operator make an error in but a single point, the favorable outcome may be compromised.

The operation for the relief of chronic obstruction of the common bile-duct has for its object the freeing of the duct; the calculi must be removed, and what is of still greater importance, the accompanying cholangitis must be allayed. It is rarely possible to force the calculi out of the common duct onward into the duodenum, or, according to the procedure of Rose, backward into the gall-bladder so as to remove them by a cystostomy. In only two or three cases have I been able to relieve the situation by so simple an operation. In almost all I have been obliged to remove the obstacle by incision of the ductus choledochus. For this purpose I make choledochotomy through an abdominal incision, and whenever possible, I add to this drainage of the hepatic duct, for the particular purpose of meeting the second indication, viz: that of allaying the inflammation.

Choledochotripsy, and the method advanced by Teale, of boring into and breaking up the stone, I cannot recommend, because the broken fragments of the stone will not always pass through the narrow papilla of the duodenum; the existing cholangitis is easily

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aggravated; and the possibility of a relapse is favored. I am well aware that here in America operations of this description have heretofore been done by preference; I am not aware whether this is still the case. At all events, basing my opinion upon my own observations, I must express myself as opposed to any such proceeding; and warn you against either intentional or accidental choledochotripsies, for the above mentioned reasons.

In the same way I look upon cholecystenterostomy as an operation of necessity only, and it is one that I have personally never had occasion to practice for obstruction of the ductus choledochus by calculus. Whoever has had the proper experience and practice will be able to find his way through the densest matting of the tissues to the ductus choledochus, and will not be obliged to avail himself of this totally inadequate anastomosis.

I have hitherto always operated at one sitting, and am not able to imagine a case that could call for a choledochotomy in two sittings. The method of laying bare the ductus choledochus through a lumbar incision is not, I think, to be commended, for in this way no opportunity is given for a proper inspection of the biliary system, and simultaneous operations on the gall-bladder, the stomach and the duodenum are rendered impossible.

In my first fifty cases I always closed the ductus choledochus with sutures; in the last hundred choledochotomies I have nearly always left the incision open and drained the hepatic duct.

Where calculi are lodged in the duodenal papilla and it is not possible to work them back into the supraduodenal portion of the duct, a papillotomy (internal choledochoduodenostomy) may be performed, as has been demonstrated by McBurney, Kocher and myself; also, access can, as has on occasion been done by Keen, McGraw, Körte, and once by myself, be gained to a calculus in the common duct through the tissue of the pancreas. It will seldom be necessary for the removal of calculi in the hepatic duct to make a special incision into the walls of this passage itself (hepaticotomy); in most cases it is possible to dislodge calculi in the hepatic duct through the incision already made in the common duct. If, together with calculi in the ductus choledochus, there be found a chronic interstitial pancreatitis, the draining off of the infected bile by means of a tube in the hepatic duct will commonly suffice to bring about resolution in the engorged head of the pancreas and to restore the normal flow of the bile. Recently, in one such case I was able to work the stones out of the common duct into the gall-

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bladder, between which organ and the stomach I then established an anastomosis.

It goes without saying that stones simultaneously present in the cystic duct and in the gall-bladder should be removed, but it would lead me too far to explain to you in what conditions I perform a cystostomy, and in what conditions I remove the gall-bladder.

Under all circumstances drainage of the hepatic duct, an operation which, as I particularly desire to emphasize, was first performed by American surgeons, is to be preferred to choledochotomy followed by suture of the duct, for the following reasons:

1. Drainage of the hepatic duct is less dangerous than choledochotomy with suture (my statistics give a mortality of three per cent. as opposed to ten per cent.), this being due to the fact that

2. Drainage of the hepatic duct is more quickly performed than the complicated operation with suture, and that

3. The almost constantly coexisting cholangitis is much more promptly allayed in the open treatment of the duct, or it is prevented from extending itself further in the liver, as I have observed it to do after choledochotomy with suture.

4. In choledochotomy with suture, even the most experienced operators in gall-stone surgery will, in fifteen per cent. of cases, leave some stone behind; in drainage of the hepatic duct there is an opportunity to remove such stones as may not make their appearance till later.

5. Relapse of the disease is therefore much rarer in drainage of the hepatic duct than in choledochotomy with suture.

6. With drainage of the hepatic duct it is possible by the insertion of laminaria tents to make this duct accessible to sounds, and also to dilate the papilla when swollen or when obstructed by a chronic interstitial pancreatitis.

From every point of view drainage of the hepatic duct is the easier and less dangerous operation, since, while I formerly had a mortality of ten per cent., this has fallen in these later years to three per cent. In my last thirty-three cases of drainage of the hepatic duct I have not lost a single patient.

It is not strictly correct, however, to speak of the mortality pertaining to a particular method of operating, since all depends upon what pathological changes are present. And so it is but natural that patients with diffuse cholangitis, complicating carcinoma of the pancreas, abscesses of the liver, and thrombo-phlebitis will die just the same whether the ductus choledochus is sewed up or left open. But

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if we are not dealing with cases of this desperate type, and if the infection is limited to the larger branches of the hepatic duct, under these circumstances the experienced surgeon need not expect a mortality greater than three per cent., provided he institutes drainage of the hepatic duct; if, on the other hand, he limits himself to choledochotomy with suture, he need not wonder that from ten to twenty per cent. of his patients die; and if he invariably practices closing of the wound without packing, the large majority of his patients will pay for his error with their lives. I cannot take this occasion to describe to you the vast advantages and the minimal disadvantages connected with the use of packing in the wound, but that surgeon was right who, when he had seen in my clinic many operations for gall-stone, stated to me as his opinion that "the great secret of my good results—he had seen thirty consecutive laparotomies for gall-stones without a death—lay in the free abdominal incision and in the generous use of gauze packing." While this view of the matter is certainly correct, I think, nevertheless, that the main success in my laparotomies is due to the very strict adherence to a rigorous asepsis. In this regard I am most exacting both with my assistants and with myself. It is thus that I have so far lost but a single patient from peritoneal sepsis after drainage of the hepatic duct.

There is no use in giving precise directions for asepsis,—that is a matter that cannot be taught with words, and one that each must learn for himself: but the man who is thoroughly imbued with the principles of asepsis, is not wholly unfamiliar with the technique of abdominal surgery, who will begin his operation with a generous abdominal incision, and will pack the wound plentifully with gauze, will learn eventually to perform drainage of the hepatic duct with as much safety as any other rather difficult laparotomy. The operation must proceed rapidly, and, whereas in my earlier choledochotomies, I took from two to three, and even four hours, I now complete almost every case of drainage of the hepatic duct in thirty minutes, and operations lasting an hour have become quite the exception.

I do not wish to leave this subject of drainage of the hepatic duct without saying a few words on the subject of the preparations for operation and the after treatment. The preparations for operation are, in general, the same as for any laparotomy, and particularly, as I have above suggested, is the carrying out of an irreproachable asepsis to be kept in mind. As patients with chronic icterus have a

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tendency to cholæmic hæmorrhages, following the example of Mayo-Robson, I administer by enema, for some days beforehand, the chloride of calcium, and accustom the patients to the use of the stomach tube, as the after treatment can seldom be completed without making use of this instrument. Since I have used the stomach tube, as it were prophylactically, I no longer encounter the acute dilatation of the stomach, which is so prone to occur after operations on the biliary tract. The after treatment is almost more important than the operation itself, and one who has not the time to devote proper pains to this should not undertake operations for gall-stones. In large hospitals the operator frequently leaves the after treatment to his assistants. These are generally younger members of the profession, who with the best will in the world take the greatest pains, but who have not had the requisite practice and experience to treat properly a patient weakened by the combined effects of the operation and of the anæsthetic. Hence, indeed, it may be that in many large clinics and hospitals the results after choledochotomy are so decidedly poor. The operator in a small private clinic, who has not such a tremendous amount of material to look after as in a large hospital, is able to devote more personal attention to his cases. The condition of a patient who has just undergone a choledochotomy demands, that he should be seen every two or three hours in order to determine whether his stomach should be washed out; whether a saline infusion should be administered; whether the dressing should be changed. The dressing after an operation for drainage of the hepatic duct is frequently a greater and more difficult piece of work than the operation itself, demanding more time than the original surgical procedure. I consider the after treatment following an operation for drainage of the hepatic duct so considerable a matter that I will not undertake an operation, if I cannot have the opportunity to superintend the after treatment at least until the first change of dressings. The flushing out of the biliary passages; the probing of the ductus choledochus; the proper renewal of the packing, are procedures which must be carried out with the greatest care, and which one cannot properly leave, without more ado, to an inexperienced assistant. Only when the latter shall have acquired the necessary experience in a large number of cases, is it proper for him to undertake the conduct of the after treatment by himself.

With this I leave the subject of chronic obstruction of the ductus choledochus by calculus, and take up the consideration of chronic

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obstruction of the ductus choledochus by tumor. Here, too, on account of lack of time must I refrain from entering upon the subjects of etiology, pathological anatomy, symptomatology and diagnosis.

Although it is possible in about eighty per cent. of cases to diagnostically differentiate between chronic choledochus obstruction due to stone and that due to tumor, it is, at the same time, almost impossible to assert whether the tumor which is compressing the duodenal end of the common duct is of benign or of malignant nature; whether we are dealing with a chronic interstitial pancreatitis or with a carcinoma of the head of the pancreas. Though we may in general admit that the cachexia in carcinoma is greater than in chronic pancreatitis, and that the disease makes more rapid progress in cancer than in inflammation, still there are cases enough that make so forlorn an impression upon the operator that the diagnosis of carcinoma appears certain. As a solace to the patient, and in order that at least something may be done, a cholecystenterostomy is performed as an operation of easy technique, and one which, even without the Murphy button, can generally be accomplished in ten minutes; the patient improves, and behold, he lives for one, or even several years, and remains in the best of condition. In such cases we have had to do then, not with a carcinoma, but with a chronic inflammation in the head of the pancreas, and because, as has been stated above, it is absolutely impossible, in the majority of cases, to differentiate diagnostically between these two forms of disease, we ought to operate, even in the face of the danger that it is carcinoma with which we have to do. In this latter case the benefit is indeed often but slight, yet in chronic pancreatitis it is extraordinarily great; persons who under any circumstances would die from cholæmia, recover and become able to work.

In carcinoma of the ductus choledochus and of the head of the pancreas it will seldom be possible to bring about a cure, though from a purely operative point of view everything is possible. The removal of the cancerous pancreas and the excision of a carcinomatous papilla have been done by Franke and by Czerny, but in both cases the patients died, or the disease recurred. One form of tumor growth on the ductus choledochus, however, does not seem to be absolutely beyond the limits of a curative operation; that is the small infiltrating cancers which develop on the supraduodenal portion of the common duct or at the confluence of the cystic and hepatic ducts, and have almost no tendency to form metastases. Six

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months ago I removed such a scirrhus by the resection of the ductus choledochus to the extent of three and a half centimeters. The ductus choledochus was freed from the portal vein with surprising ease; the gall-bladder together with the cystic duct were then removed, and the hepatic duct was implanted into the duodenum. This is, indeed, the first case of extensive resection of the common bile-duct, and the first hepaticoduodenostomy. I have described this hitherto successful case in detail in the Münchener medicinische Wochenschrift.

In closing my address, I beg leave to lay down the following propositions as the conclusions to be drawn from it:—

1. The treatment of *acute* obstruction of the ductus choledochus by calculus belongs, with few exceptions, to the province of internal medicine.

2. In *chronic* obstruction of the duct by calculus, when complete and permanent latency is not achieved, surgical assistance is required. The operation must not be put off too long. As a rule one should not wait longer than three months after the initial symptoms of obstruction of the common duct.

3. Choledochotripsy is to be altogether rejected, and cholecystenterostomy has a very limited application. In the place of choledochotomy with suture, drainage of the hepatic duct is to be practiced. When calculi cannot be dislodged from the duodenal papilla the method of McBurney is to be considered. Incision into the hepatic duct is rarely necessary.

4. So long as the disease is not complicated with diffuse cholangitis, abscess of the liver, carcinoma of the pancreas, etc., the operation is not attended with particular danger and the mortality is about three per cent. When performed late, i. e., when severe infection is already present, the operation can seldom be made to yield the benefits that otherwise may be expected from it.

5. The most careful attention must be devoted to the after treatment.

6. In chronic obstruction due to tumor (carcinoma of the ductus choledochus, carcinoma of the pancreas) surgical treatment alone can be considered.

(a) This must in most cases consist in a merely palliative operation.

(b) In small carcinomata in the middle portion of the ductus choledochus a radical operation is possible.

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(c) In benign tumors of the pancreas (chronic interstitial pancreatitis) an operation may bring about permanent recovery.

Gentlemen, I do not know what are considered in this country to be the indications for operation in chronic obstruction of the ductus choledochus. I assume that the conditions here are not greatly different from what they are among us in Germany, to wit, that among practitioners of internal medicine there is a good deal of reluctance to recommend operation. Surgeons and physicians are oftentimes bluntly opposed in their estimates of the indications for operation, but without harmony between the representatives of the two sister branches of our art, a really advantageous treatment of cholelithiasis is impossible, and particularly in chronic choledochus obstruction is harmonious coöperation an indispensable factor. I therefore address to you this word of admonition,—when you have a patient in whom there has developed the typical picture of chronic obstruction of the common bile-duct, whom you have treated in vain with Carlsbad salts, olive oil, eunatrol or other such remedies, bring a good surgeon into your counsels so that he may prove the case, by removing the obstacle with his aseptic knife, and to the patient, foredoomed to death, give back that life, which is, after all still so dear.

If this my message be not altogether unheeded, my address will have fulfilled its object: I shall not have crossed the ocean in vain, and can hasten back to my home with happy and contented spirit.

The following papers on the surgical treatment of gall-stone diseases have been published by myself and my assistants. The most important are marked with an asterisk.

*[1] Kehr, Eilers, Lucke, Bericht über 197 Gallensteinoperationen aus den letzten 2⅔ Jahren, *Arch. f. klin. Chirurgie,* 58. Bd., Heft 3.

[2] Wie, wodurch und in welchen Fällen von Cholelithiasis wirkt eine Karlsbader Kur und warum gehen die Ansichten des Chirurgen und des Karlsbader Arztes in Bezug auf Prognose und Therapie der Gallensteinkrankheit so weit auseinander? *Münch. med. Wochenschr.,* 1898, No. 38.

*[3] Die Resultate von 360 Gallensteinlaparotomien unter besonderer Berücksichtungen der in den letzten 2 Jahren ausgeführten 151 Operationen, *Samml. klin. Vorträge von Volkmann,* No. 225, Okt. 1898.

[4] Die behandlung der calculösen Cholangitis durch die directe Drainage des Ductus hepaticus, *Münch. med. Wochenschr.,* 1897, No. 41.

*[5] Die chirurgische Behandlung der Gallensteinkrankheit, Berlin, 1896, *Fischer's med. Verlag* (H. Kornfeld).

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*[6] Ein Rückblick auf 209 Gallensteinlaparotomien mit besonderer Berücksichtungen gewisser anderweitig selten beobachteter Schwierigkeiten bei 30 Choledochotomien, *Arch. f. klin. Chir.*, Bd. 53, Heft 2.

*[7] Die Entfernung des eingeklemmten Gallensteins aus dem Ductus cysticus durch Incision dieses Gangs, *Arch. f. klin. Chir.*, Bd. 48, Heft 3 (Chir. Congr. 1894) und *Berl. klin. Wochenschr.*, 1894, p. 536.

*[8] Neue Erfahrungen auf dem Gebiete der Gallensteinchirurgie, *Berliner Klinik*, Heft 78, Dez. 1894.

*[9] Zur Chirurgie der Gallensteinkrankheit, *Deutsche Zeitsch. f. Chir.*, 38. Bd., p. 321, 1894.

[10] Zur Chirurgie der Gallensteinkrankheit, *Berl. klin Wochenschrift*, 1893, No. 2.

[11] Ueber einen durch ideale Cholecystotomie geheilten Fall von Schussverletzung der Gallenblase, *Ctrbl. f. Chir.*, 1892, No. 31.

[12] Operativer Beitrag zum Aufsatz des Herrn Dr. Hochhaus in No. 17 dieser Wochenschrift. Ueber Magenerweiterung und Duodenalstenose, *Berl. klin. Wochenschr.*, 1891, No. 22.

[13] Zur Chirurgie der Gallenblase, *Vortrag, geh. im Aerzte-Verein des Reg.-Bez. Magdeburg*, 20. Okt. 1891.

*[14] Anleitung zur Erlernung der Diagnostik der einzelnen Formen der Gallensteinkrankheit, Berlin, 1899, *Fischer's med. Verlag*. Translated into English by W. W. Seymour, and published by P. Blakiston's Son & Co., Philadelphia, 1901, under the title: Introduction to the differential diagnosis of the separate forms of gall-stone disease.

*[15] Die Verletzungen und chirurgischen Erkrankungen der Leber, der Gallenwege und der Milz, *Handbuch der practischen Chirurgie* von v. Bergmann, v. Bruns, v. Mikulicz. Ferd. Enke, Stuttgart.

[16] Wie gross ist heute die Mortalität nach Gallensteinoperationen? *Münch. med. Wochenschrift*, No. 23, 1901.

*[17] Wie verhält es sich mit den Recidiven nach unseren Gallensteinoperationen? *Arch. f. klin. Chir.*, 61. Bd., Heft 2.

*[18] Ueber Recidive nach Gallensteinoperationen, *Berliner Klinik*, Heft 148, Berlin, Okt. 1900.

*[19] Die chirurgische Behandlung der Gallensteinkrankheit, *Deutsches Klinik* von v. Leyden, Berlin, Urban und Schwarzenberg, 1901.

[20] Eine seltene Anomalie der Gallengänge, *Münch. med. Wochenschrift*, No. 6, 1902.

*[21] Ein Rückblick auf 720 Gallensteinlaparotomien unter besonderer Berücksichtigung von 90 Hepaticusdrainagen, *Münch. med. Wochenscrift*, 1902, No. 41, 42, 43.

[22] Ueber den plastischen Verschluss von Defecten der Choledochuswand durch Netzstücke und durch Serosa-Muscularislappen aus Magen oder Gallenblase, *Arch. für klin. Chir.*, Bd. 67, Heft 4.

*[23] Beiträge zur Bauchchirurgie von Kehr, Berger und Welp, Berlin, *Fischer's med. Verlag*, 1901 (Casuistik von 84 Gallensteinlaparotomien).

*[24] Beiträge zur Bauchchirurgie, Neue Folge, von Kehr, Berger und Welp, Berlin, *Fischer's med. Verlag*, 1902 (Casuistik von 95 Gallensteinlaparotomien).

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*[25] *Zwölfter Jahresbericht der Kehr'schen Privatklinik*, 1902, Guben, Albert Koenig. (Ueber gleichzeitige Erkrankungen der Gallenblase und des Wurmforsatzes.)

*[26] Ueber einen Fall von ausgedehnter Resection des Ductus choledochus und hepaticus wegen Carcinoma choledochi mit nachfolgender Ectomie der Gallenblase und Hepatico-Duodenostomie, *Münch. med. Wochenschrift*, 1903, No. 3.

[27] Die Verwendung der Gelatine zur Stillung cholämischer Blutungen nach Operationen am Gallensystem nebst Bemerkungen über Poppert's wasserdichte Drainage der Gallenblase, *Münch. med. Wochenschrift*, 1900, No. 6 u. 7.

*[28] Dr. Berger: Die Hepaticusdrainage, *Arch. f. klin. Chir.*, 69 Band, p. 299 (Festschrift für von Esmarch), 1903.

*[29] Derselbe: Trauma und Cholelithiasis (*12. Jahresbericht der Kehrschen Privatklinik*, 1902, Verlag von Albert Koenig, Guben).

[30] Derselbe: Ergebniss bakteriologischer Untersuchungen der bei und nach Gallensteinoperationen gewonnenen Galle, Beitrag. zur Bauchchirurgie von Kehr, Berger, Welp, Berlin, *Fischer's med. Verlag*, 1901.

*[31] Dr. Herbst: Pancreatitis chronica interstitialis oder Pancreascarcinam? (*12. Jahresbericht der Kehr'schen Privatklinik*, 1902, Verlag von Albert Koenig, Guben.)

Discussion.

Dr. Frank Billings.—I desire to speak of the diagnosis more especially of gallstones in the earlier stages. The surgeon has by the great number of operations done in the last few years so enlightened us in the diagnosis that it can be more readily made than formerly, but in spite of this fact we are in many cases absolutely unable to make a rational diagnosis. The most prominent symptom referred to by writers of the present day is pain, and this pain is usually in the region of the gall bladder apparatus. It is not always severe, nor always colicky in character, and points of tenderness may be present without pain. Tenderness may be elicited in patients whose abdominal walls are not too thick, and the phenomenon which I have noticed in almost every case, is the reflection of the tenderness elicited by pressure within the gall bladder region towards the epigastrium, which may explain the reason for pain in the region of the stomach when gallstones exist. Jaundice does not exist unless the gallstone has escaped from the cyst and has passed into the common duct, causing obstruction. Jaundice may also occur from the infection passsing from the gall bladder through the gall ducts into the liver. We should not take this pain or this tenderness as a sure sign of gallstone, for there are other conditions which will produce pain in this region. Within one year two patients have come to me who have been operated upon for cystic

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gallstones without the stones having been found, both suffering from gastric crises due to locomotor ataxia. Floating kidney will also produce similar symptoms in this region, and an inflamed appendix may refer pain to the gall bladder region. More than one case has been operated upon for gallstones when the appendix was the seat of trouble. In spite of this fact, if one is careful in his examination he will be able to separate these conditions from that of pain due to gallstones. Gallstones to my mind are in one sense harmless, and do not present symptoms which enable us to make a diagnosis until there is infection of the gall bladder or ducts. When we are able to make a diagnosis of gallstones the case it seems to me is usually already a surgical one and is no longer a medical disease. If once a diagnosis is made and we can elicit the fact that gallstones have repeatedly occurred in the past I think that operation is indicated at once. I feel this so strongly that I tell my patients so and emphasize the fact that they must take the responsibility if not operated. I am in favor of first trying to get rid of the infection by proper food, drink, and in the case of women, adjustment of the dress and proper respiratory exercise, before advising operation, and if I fail in that, I then say, find the proper surgeon.

Dr. George Dock:—There are so many aspects to this subject that one feels compelled to attempt to cover only a part, and I shall therefore limit myself to one or two points. There is a class of cases of disease due to gallstones that is easily recognized, and only carelessness or ignorance would prevent us from sending these cases to the surgeon. Unfortunately many of them do not go to the surgeon, and this is partly due to the ignorance of the beneficial results to be obtained by surgical treatment on the part of both patient and physician. The papers read here to-day will go far towards improving this and removing ignorance. In some cases all the ordinary symptoms may be absent, or those present may resemble appendicitis or renal colic. Most of them, as has been said, may be easily separated by a careful examination, but some cases will still remain obscure, and will have to be cleared up by the surgeon. Some of these cases have no history of gallstone disease, and many of them do not come to autopsy at all, so that the pathologist does not have an opportunity of studying them. More has been learned from the surgeon than from the pathologist in these cases, and I think still more will be learned in this same way. I have

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been particularly impressed with cases of stomach disease that simulate gallstone disease, and the diseases of the biliary tract involving the stomach. Valuable time may be lost by temporizing in cases of this kind. A brief recital of a case illustrates this. A patient came to me recently with very marked dilatation of the stomach without any history pointing to the cause. It seemed probably one of latent ulcer of the stomach, followed by cicatricial contraction, and the condition was almost desperate. The case was at once referred to the surgical clinic for treatment, and a few days before the operation, while the stomach was being washed out a gallstone came up with the stomach washing. Although confronted with this evidence of disease the patient could still recall no symptoms or tenderness in the region of the gall bladder. But examination before this had shown a resistance in this region, but a most careful cross examination failed to elicit any information from the patient. The patient finally came to operation, which, unfortunately, was fatal. It was found that he had old and very extensive disease of the gall bladder and cystic duct, so that they were almost unrecognizable. The stone that escaped into the stomach during life was only one of a number that lay just at the orifice of the duct, a quarter of an inch below the pylorus, while the obstruction was just beyond the pylorus and was due to kinking. In another case the condition of the stomach was so similar that I hesitated to make a diagnosis, but a cross examination in this case elicited a history of mild attacks of jaundice, long before, which had been forgotten. Operation in this case revealed gallstones in a contracted gall bladder, kinking of the pylorus, and dilatation of the stomach. Operation in this case (by Dr. C. B. Nanerede), was entirely successful. Such cases illustrate the need of more frequent recourse to surgical measures, and the importance of at least a thought of the biliary tract in planning operative treatment. However, these facts have been fully brought out by the previous speakers.

Dr. Henry Sewell:—My remarks will be confined to a consideration of some of those physiological conditions whose modification leads to the formation of gallstones.

It may be assumed that the bile is a continuous secretion which, collecting with varying rapidity within the ducts of the liver may be, as held by Copeman and Winston,[1] rhythmically impelled thence by contraction of the slender musculature of the larger bile ducts.

[1] Jour. Physiology, X, 1889, p. 213.

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It is worth considering how the bile gets into the gall bladder during the intervals between its outpourings into the intestine. The hepatic duct and the common duct form a nearly straight, continuous tube, and the bile descending the former would seem to find no obstacle to its progress until it reaches the region of the sphincter muscle of the common duct at the entrance of the latter into the intestinal wall.[1] While this muscle is in action the common duct is probably filled with nearly stagnant bile, and the supply to the gall bladder must be due either to a current from the hepatic duct which penetrates but a slight distance into the already filled common duct or else, which seems less probable, the common duct must also by rhythmic antiperistalsis empty itself into the cystic duct. The cystic duct communicates with the common duct by a pore-like opening, perhaps less than two millimeters in diameter in the human subjects; a thin projection of mucous membrane bars it from the outlet of the hepatic duct.

In my dissections the structure of the wall at the confluence of the cystic and hepatic ducts is noticeably stiffer than that of the common duct immediately contiguous, so that it can be seen how a slight, positive internal pressure would distend the common duct without collapsing the opening of the cystic duct, and thus keep the latter patent.

When the common bile duct is slit longitudinally in its peripheral region, its mucous membrane from the point of its entrance into the intestinal wall to the opening of the pancreatic duct, distant about half an inch, is relatively rough and corrugated as contrasted with the smooth lining of the common duct elsewhere. This is a point I do not know to have been hitherto observed. The anatomical fact suggests that the sphincter muscle of the common bile duct during its contraction keeps the whole of the intra-intestinal portion of the duct free from bile and thus prevents the fluid from penetrating the pancreatic duct; the latter result would be expected were the sphincter action confined to the very extremity of the common duct.

There are sound reasons for believing that the entrance of bile into the intestine is by way of intermittent jets brought about by a rhythmic reflex action whose usual stimulus is the healthy acid chyme from the stomach (or, more specifically, its proteid and fatty constituents), which acts on afferent nerves,[2] probably fibres from

[1] Cf. W. F. Hendrickson, John Hopkins Hosp. Bull., Sept.-Oct., 1898.

[2] Bruno, Arch. des sciences biol. de St. Petersb., t. vii, p. 87. (Quoted by Howell, Am. Text b. Physiology, vol. I, p. 249.)

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the vagi, in the mucous membrane of the duodenum; the resulting reflex consists in a simultaneous inhibition of the sphincter muscle at the termination of the common duct and a contraction of the muscles of the gall bladder.[1]

Clinicians and pathologists have made it sufficiently clear that the dangers of gallstone disease depend upon bacterial invasion of the gall bladder or ducts, if, indeed, such invasion is not the necessary precursor of every gall-stone formation.

It is proper to seek for means by which it may be supposed the bile mass is normally guarded from such infection,—for it is conceded on all hands that stagnant bile invites the multiplication of pathogenic germs within it. As regards the entrance of micro-organisms from the intestine, the supposed sphincter action of the muscles covering the terminal one-half inch or so of the common duct must form a useful barrier. But the body must have to deal more or less constantly with micro-organisms which have already penetrated the biliary tubes. As to the ducts within the liver itself, the penetration of foreign bodies in that direction is no doubt prevented under normal conditions by the continuously outflowing stream with its occasional accelerations.

When bacteria have once run the blockade of the sphincter of the common duct they fall, according to the position taken above, into a practically stagnant column of bile; and when they have penetrated as far as the origin of the common duct it may well be granted that the invading micro-organisms, during the periods when the choledochus sphincter is closed, are swept into the gall bladder by the current of bile there collecting. Whether the voluminous valve of Heister has any value as a bacterial screen to protect the gall bladder is a question apparently untouched by investigators. Admitting that infectious material has actually penetrated to the gall bladder, the physiological citadel is as yet by no means captured by the enemy. For, supposing the reflex mechanism for bile explusion to be in good condition, ever and anon the choledochus spincter is relaxed, the gall bladder, and possibly the large ducts, contracts and the cystic and common ducts are flushed by a sharply projected stream of bile. Again and again, we may suppose, during each digestive cycle these channels are washed by a sterile and even slightly antiseptic fluid, offering almost ideal conditions for surgical cleanliness.

[1] Doyon, Arch. de physiol. norm. et pathol, 1894, p. 19. (Abstr. Hermann's Jahresbericht ü. Physiologie, M. F. III, S. 82.)

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Even when infection has turned the normal into pathological conditions, the frequent and early bilious vomiting may possibly prove a useful aid to self-protection. It seems plausible, indeed, that an important, if not the principal, function of the gall bladder is to serve as a flush tank for the peripheral biliary system. A natural suggestion from the foregoing is the suspicion that atrophy of the gall bladder, and even its extirpation, may predispose to the condition of cholangitis, because of the failure of the flush tank action.

There is obviously a fatal impediment to the self-cleansing function of the bile discharging apparatus when for any reason there is undue stagnation of the bile. It is well known that all factors, such as the habits of dress, relations of mealtimes, etc., hindering the fullness and frequency of bile movement, distinctly predispose to gallstones. Or, again, when, as seems sometimes to be the case, pathogenic bacteria are separated from the blood in the liver and pass down the hepatic duct the gall bladder is continually bathed with an infective fluid which offers a continual menace to health.

While it is sufficiently clear that the extreme dangers of gallstone formation result from infection and while there is even evidence that without infection there is no stone formation, there is reason to believe that the biliary apparatus has a considerable power of protecting itself against the precipitation of stones even in the presence of pathogenic germs, and of adjustment to the morbid condition when once it has arrived. The findings of the surgeon who opens the gall bladder, especially the fact that stones are prone to occur in different sets of sizes, point to the conclusion that gallstone disorders, for the most part, fall in the class of self limited diseases. In any particular subject infective processes within the gall bladder may give way an indefinite number of times to the protective powers of the body.

The gall bladder itself is, in the vast majority of cases, undoubtedly the site of the stone formation. The anatomy of the region of the outlet of the gall bladder and of the lumen of the cystic duct seems peculiarly adapted to prevent the expulsion into the duct of any foreign particles except such as are of minute size. It seems as though a process of natural, if pathological, selection had adapted the gall bladder apparatus to disarm the morbid process of its dangers by confining the stones formed by it harmlessly within the gall bladder.

Further evidence in the same direction is furnished by the curious fact that atrophy of the gall bladder is so apt to occur when stones

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are confined in that viscus and thus put out of question the dangerous chance of their extension into the ducts. Moreover, it seems fair to presume that the cessation of the stream of bile into the atrophied bladder, combined with more or less stenosis of the cystic duct, must have an influence in preventing reinfection of the stagnant contents of the organ.

Too little is known of the mechanism of the bile-forming apparatus for us to discuss definitely the relations of its functions to the formation of gallstones. Yet we believe with reason that the bile salts are the normal solvents of cholesterin[1] which composes the majority of gallstones, and it seems probable that a normal hepatic metabolism, at least as regards the production of bile acids, is distinctly helpful in keeping in solution material which would otherwise be precipitated. Moreover, as physiology teaches that from the bile secreted into the intestine the salts are again absorbed, presumably to undergo an internal circulation, it is obvious that a healthy action of the resorbing apparatus is essential to the protection of the bile from precipitation. Again, the cholesterin excreted by the liver cells probably represents metabolism of the living tissues at large and its amount therefore may be assumed to depend upon the state of health of the whole organism. The cholesterin and other products arising from inflammation of the mucous membrane of the gall bladder under the influence of infection must depend in their amount and character on the physiological state of that membrane and its powers of resistance.

Undoubtedly important as are the general body metabolism and the intrinsic resistance powers of the biliary mucous membrane to gallstone formation, their relations are at present too obscure for profitable discussion. Turning, however, to the study of conditions which determine the admission of microbes to the biliary tract, it seems reasonable to suppose that any circumstance that restrains the frequent and abundant flushing of the common bile duct would lead, through the stagnation of bile within it, to the penetration of microorganisms and infection of the gall bladder.

Unfortunately here, too, we are forced to rely upon probabilities to support our contention. Since we have seen that the normal stimulus to the reflex expulsion of bile from the gall bladder is the acid chyme of the stomach, it is permissible to assume that a healthy condition of the stomach, both as to its secreting and motor power, is one of the normal safeguards against the formation of gallstones.

[1] Gamgee, Physiological Chemistry, vol. II, p. 339.

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The presumption is also obvious that a physiological condition of the mucous membrane of the duodenum is intimately related to the normal action of the afferent nerves entering into the reflex arc concerned in bile expulsion, as well as to the efficiency of the sphincter muscle of the common bile duct.

The extension of a duodenal catarrh into the duct would obviously interfere with the outflow of bile, and at least to this extent favor infection of the fluid. In other words, there is reason to believe that a morbid digestion in stomach and intestine is a predisposing cause to the formation of gallstones.

The paroxysms of gallstone disease seems to me to be separable into two groups of symptoms, namely first, those due to direct irritation by stone of an inflamed mucous membrane, and second those belonging distinctly to the family of gastro-intestinal disorders.

The latter symptoms may sometimes be repeated after the removal of gallstones by operation, and it is open to suspicion that this variety of symptoms in cholelithiasis is not always the reflex and referred nervous results of stone irritation, but frequently has its origin in intrinsic gastro-intestinal disorders that have remotely led to the gall stone disease and are characteristically bound up with it.

Dr. E. G. Janeway, of New York:—In my opinion it is very important in cases of obstruction by stone that the character of the food taken by the patient should be under the control of the physician. I would not raise this point were it not for the fact that I recently saw a case of complete obstruction where the physician in charge, who was a well-versed man, and made somewhat of a special study of these cases, told me that the bile flowed into the intestine. The diagnosis, therefore, could not be complete obstruction, and cross-questioning of the patient very closely elicited the fact that he had been eating very largely of spinach, which had stained the passages green. I feel, therefore, that in making a diagnosis the character of the food should be taken into account. I have seen two cases operated upon for gallstone obstruction, where the disease was ulcer of the duodenum. I thought these two points might be of some interest.

I would like to mention that Dr. Brewer omitted the name of Monneret as one of the first to call attention to the intermittent fever of biliary obstruction.

Mr. B. S. A. Moynihan, Leeds, England:—Anything I might have to say upon a subject such as this would be merely in the char-

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acter of commending the learned remarks made from the platform. I shall not be able to decide when I get away from here which has been the greatest treat of my life, to-day or yesterday, as on both occasions I have had the very greatest possible benefit from the experience of those selected to talk. We have a considerable number of cases of gallstone disease in England, and I might say that this is the trend of our recent surgical experience. Dr. Mayo has mentioned one point, and that is the performance of operations upon the common duct by an incision which we have recently employed. Operations upon the common duct used to be considered extremely serious, but our mortality recently has not been more than three or four per cent. We have attributed this improvement to the kind of incision which we have employed, through which we are able to see the gall bladder and pull out through the wound about one-third of the liver. One can get the common duct open and suture it if necessary. This little detail in the operation has given us very considerable satisfaction, and has made possible an operation upon the common duct in twenty or thirty minutes. We are being driven oftener and oftener to an inspection of the gall bladder, and I am glad to hear that this is the trend of surgical methods here. I think that sometimes where cholecystotomy has been performed there has not been complete abolition of all the trouble, as patients have complained of an uneasiness in the old scar. For many reasons we have been driven to the performance of the operation of cholecystectomy, and our alterations have lain chiefly along this line. We have had more facilities for operating upon the common duct, and we are better satisfied with our results.

I was called upon quite unexpectedly, and I desire to express my deep sense of gratitude for this very profitable afternoon.

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THE PRESIDENT'S ADDRESS.

BY W. W. KEEN, M.D., LL.D., F.R.C.S. (HON.)

Professor of the Principles of Surgery and of Clinical Surgery, Jefferson Medical College Philadelphia.

THE DUTIES AND RESPONSIBILITIES OF TRUSTEES OF PUBLIC MEDICAL INSTITUTIONS.

The value of occasional and stated gatherings of the principal leaders of medical thought in the various special departments is acknowledged by all. Certainly those who have attended this Congress, now held for the sixth time, have felt its broadening influence. We are all apt to become narrow when we are devoted heart and soul to one specialty, be it medicine, surgery, physiology, ophthalmology, or any other. When we meet nearly all of the more prominent men in cognate interrelated branches of medicine in Washington every third year, we are sure to find that there are as interesting and as important questions in other specialties as there are in our own; and, moreover, we are sure to find that there are men of as acute intelligence, wide reading, and original thought in other than our own departments whom it is our pleasure to meet, and whose acquaintance becomes not only valuable for what we find them to be, but because of the stimulus that they give to our own thoughts.

Ordinarily the Presidential address has been devoted to some special professional topic. My first idea was to select such a subject for to-night, but as I was absent from the country when I received the very highly appreciated notice of my selection, I asked the members of the executive committee for suggestions, being sure that their united judgment would be better than my own. I was very glad when they proposed the topic upon which I shall address you, partly because it is different from the usual type of such addresses, and partly because it seems to me appropriate to the present time. I shall, therefore, give the time at my disposal to presenting to you some thoughts on "The Duties and Responsibilities of Trustees of Public Medical Institutions."

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Before entering upon my topic I beg to state explicitly that what I may say is offered in no spirit of unfriendly criticism, but only by way of friendly suggestion. I have been too long and too intimately associated with scores of such trustees not to know that they are almost without exception generous, self-sacrificing, giving of their time and money and thoughtful care without stint and often sacrificing personal convenience and comfort for the good of the college or hospital which they so faithfully serve. Anxious to discharge their trust to the best of their ability, I am sure they will accept these suggestions, the fruit of forty years of personal service as a teacher and a hospital surgeon, in the same friendly spirit in which they are offered.

There are two such classes of institutions to be considered: (1) Medical colleges, and (2) Hospitals, whether they be connected with medical schools or not.

There is, it is true, a third class of trustees for a wholly new kind of medical institution which has arisen as a modern Minerva Medica, born full-armed for the fray. Of this class we have as yet but a single example—the Rockefeller Institute for Medical Research. Akin to it are laboratories for special investigations, such as the two Cancer Laboratories in Buffalo and Boston. But the Rockefeller Institute is so recent, and its scope at present necessarily so undetermined, that I would not venture to consider the duties of these trustees, and I am sure their responsibilities are adequately felt by them. Moreover, their admirable selection of a Director for the institution is the best pledge of a future wise administration. I heartily congratulate the Profession and America upon the establishment of so peculiarly useful an institute. Its founder has wisely left its work unhampered saving as to its general purpose, and the whole world, and especially the United States, will soon be his debtor for researches and discoveries that will abridge or even abolish some diseases, shorten sickness, prolong life, and add enormously to the sum of human happiness. Could any man of wealth by any possible gift win for himself a higher reward or a happier recollection when he faces the future world?

Though not a medical institution, I cannot refrain also at this point from expressing not only for myself, but for you, our hearty appreciation of what the Carnegie Institution has done for medicine in the reëstablishment of the *Index Medicus*. This publication is essentially and peculiarly American in origin, but its usefulness is worldwide. It aids alike an author in Japan or in India, in Europe

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or America. It is one of the best and wisest undertakings of this lusty educational giant. But to ensure the permanent publication of the *Index Medicus* the profession must show that it really values this generous gift. Unless the *Index* finds a hearty support in the profession abroad and especially at home, we can hardly expect the continuance of this unique and invaluable publication. May I earnestly ask, therefore, of this audience of the chief medical authors of the United States that each one will demonstrate his appreciation by an immediate subscription to the *Index Medicus*.

There are some matters common both to the medical college and the hospital which may be considered together. The most important of all these is the cordial and hearty coöperation of the medical men connected with the college or hospital and the boards of trustees. In order to ensure this the members of each body must be acquainted with each other. I have known of instances in which if a professor in the medical school ventured to suggest any changes as to its management, or even to state his opinion as to the qualifications of a candidate for a vacant professorship, his suggestions were resented as an interference instead of being welcomed as a means of valuable information. I take it for granted that we should not offer such suggestions after the fashion of a partisan either of a man or a measure, for the advancement of a friend or to the disadvantage of an enemy, but solely for the good of the institution with which we are connected. He who would endeavor to foist a friend upon an institution *because* he is his friend, and in spite of the fact that a rival is the abler man and better fitted for the position, is just as false to his duty, to his college, or to his hospital, as the trustee who would vote for the less desirable man on the ground of personal friendship, or of association in some society, church or other similar body. Of all these influences, that arising from membership in the same religious body is, I fear, the most frequent and yet most absolutely indefensible. What one's theological opinions are has no more to do with his qualifications for a professional or hospital appointment than his opinions on protection as against free trade, or whether Bacon or Shakespeare wrote Hamlet.

I have always honored one of a board of trustees, who was an old personal friend of my father's and who had known me from boyhood, yet who in my early professional career, when I asked for his vote for an important hospital appointment, had the manly courage to tell me that he thought a rival, who was older and more experienced, was the better man for the place and that he should,

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accordingly, vote for him and not for me. I confess it was at the time a bitter disappointment to me, but I never had so high an opinion of my father's friend as after he denied me his vote.

There should be, in my opinion, but two questions asked in considering the election of either a professor or a hospital physician or surgeon. First, which one of the candidates for the place has the best qualifications from the medical point of view? This should include not only his scientific knowledge, but his ability practically to impart or to apply that knowledge. Secondly, are his personal qualifications and character such as to make him a desirable incumbent of the position? It must be remembered that a man may be scientifically and practically an extremely able man, but of such a quarrelsome disposition, or the unfortunate possessor of some other similar personal disqualification, as to make him a most undesirable member of a staff. The personal equation may be quite as important as the scientific qualification. Of course his personal moral character should be above reproach. To place a drunkard or a libertine in a position of so much responsibility and influence is to abuse a trust. No patient should be confided to the care of such a man and still more no such man should be made an instructor of young men, upon whom his influence would be most disastrous.

It is often extremely difficult for a layman to reach a correct conclusion as to the qualifications of medical men for college or hospital appointments, because of the confident, yet conflicting, statements of their friends. But there is apt to be a certain clear partisanship in such statements which betrays the purpose of the speaker. Especially will this be so if he advocates the election of A or B on the lower grounds of friendship, social position, or for other similar motives. The man who is advocating the best man because he *is* the best man has the stamp of sincerity upon every word.

Perhaps the most striking example I can adduce of such an unfortunate misjudgment is Dr. S. Weir Mitchell, who was denied a professorship in both the medical institutions of his native city, thus depriving them of the most brilliant medical genius that America has produced within my personal recollection. For him it is now a matter of indifference, and for American literature it has been a gain. But for medicine, and especially for physiology, it was an immense loss. Both of his rivals were estimable, worthy gentlemen who held an honorable position in the profession, it is true, but Mitchell is a genius. "Eclipse was first; the rest were nowhere."

One of the best methods of bringing the medical board and the

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board of trustees into more intimate contact would be to have the dean or a committee of the faculty, or, in a hospital, if the staff is not too large, the whole staff invited to the meetings of the board. Here I can speak from personal experience. At the Orthopedic Hospital and Infirmary for Nervous Diseases in Philadelphia, there are three surgeons and three physicians. These members of the medical staff are invited to meet with the board of managers at each monthly meeting, excepting the annual meeting, when the medical staff is elected. They are free to express their opinions on any topic relating to the management of the hospital to which their judgment may contribute something of value, but when a decision is taken they have no vote. It is purely in an advisory capacity and for the purpose of giving and receiving information that they are present. The plan works exceedingly well. When economy is necessary in the hospital, the staff is fully acquainted with the fact and can coöperate with the trustees; when expenses have run up from carelessness in the wasteful use of dressings or appliances, a halt is called; when, alas, very rarely, the treasurer is all smiles, and plans for the extension of the hospital, or the installation of some new addition to the plant is contemplated, their knowledge as to the necessity, for instance, of a hydrotherapeutic or an *x*-ray plant, or a new operating room, is the greatest possible value. Nothing but good, in my opinion, can come from such personal coöperation.

One of the difficult questions which boards of trustees have to face is whether there shall be a fixed age at which a college professor or a hospital physician or surgeon shall retire from the active duties of his post. I firmly believe that they should fix such a retiring age in the interest of the students and the patients. As age advances, a man's opinions and his practice become "as petrified as his arteries." He is incapable of constant study, of adding to his knowledge or of keeping up with the feverish strides of medicine. He ought then to be relieved of his cares and his duties. If no rule exists, he is allowed to continue his inefficient or even disastrous work, or by some harsh suggestion is compelled to give place to another more competent man. A rule is a condition accepted when he is appointed, and just as in the army and navy, when an officer reaches 64 or 62 years of age he is retired on reduced pay, and because it is a rule he does not feel hurt or humiliated; so in a college or a hospital, when time and the rule bring us to the period when we must gracefully retire, no one's reputation is injured or his feelings lacerated.

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I have ascertained that the following rules are in force in some of the larger institutions:

At Harvard, the age when a professor may request to be retired is 60, provided he has been in the service of the university for 20 years, with a reduced pay ranging from one-third to two-thirds of his salary. At 66 he may be retired by the President and Fellows partly or wholly. The details of the plan are admirably arranged.

At Chicago, while no plan is yet in force, largely, I presume, because of its recent establishment on the present basis, such a plan will soon be made operative.

At Columbia the retiring age, after 15 years of service, is 65, either at the request of the professor or upon motion of the trustees, and on half pay.

At Yale the retiring age is 65, after 25 years of service, and on half pay, but the retirement is not compulsory. It will probably be made compulsory before long.

At Cornell the retiring age is 70, but the Pension Fund will not be available until 1914. The retiring pension will then be $1,500.

At the University of Pennsylvania and at Johns Hopkins no retiring age is fixed.

The only hospitals I know of in which a retiring age is fixed, are the Massachusetts General Hospital and the Boston City Hospital. At the former the compulsory retiring age of the surgeons is 63, and of the physicians 65. At the Boston City Hospital the visiting surgeons are retired at 65, but the physicians, gynecologists, and all the other medical officers continue in service indefinitely—a very curious anomaly.

These varying but in the main identical provisions, when any exist, show the trend of thought and practice. They generally apply to the medical department, except that in case a professor is engaged in the practice of his profession and so has a private income, the provision for continuing a portion of his salary does not apply. This is right and fair. Of course, in all hospitals where there are no salaries, no provision as to reduced salary would obtain.

The point I wish to emphasize is, however, that the age limit (which in my opinion should be 65) should be *compulsory* and so not be invidious in any given case. It will be objected that not a few men are in full intellectual and physical vigor at 65, and it will be a detriment to the institution to lose their services when their ripe experience and admirable teaching are most desirable. I admit it. But for every one such case of harm done by compelling a man

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to stop, there are a score of instances of men who are doing vast injury by their inefficiency. Moreover, in the very few cases in which it might be allowable, as boards of trustees make rules they can unmake them, and in special cases they could pay a graceful compliment and preserve to the institution their exceptional men by extending the limit to 70. In no case can I think it wise to go beyond this limit.

In some of the universities I have quoted a sabbatical year of rest or study is allowed a professor. He is put upon half pay and his place is filled by a temporary substitute, who receives the other half of his salary. I believe that in present conditions this should not be applied to medical faculties, for nearly all of the professors are in active practice and take sufficiently long summer holidays. These latter are often spent in observation and study abroad—a most useful and remunerative employment of a holiday—and serve the purpose of the sabbatical year for men whose entire time is given to their teaching. In hospitals it certainly should not apply.

One of the recurring questions in hospital and college management is whether there should be a certain number of doctors on the board. I know that there is a wide diversity of opinion upon this point. My own belief is that a small proportion of well chosen medical men is a distinct advantage in such boards of trustees. I have said a "small proportion," for it should not be, I think, larger than probably 20 per cent.; and I also said "well chosen"; that is, they should be men of large mental calibre and executive ability. It should be distinctly understood, if not indeed absolutely expressed, in institutions in large cities at least, that any physician or surgeon placed upon such a board should never be eligible, even by resignation from the board, for a position on the faculty or the medical staff. In small towns the lack of suitable persons for hospital trustees and members of the hospital staff might make it desirable not to institute such a rule.

Moreover, such medical men should be selected for trustees as by their mental training, social relations, and personal character would be, so far as it is possible for human nature to realize such a position, absolutely free from influences arising from personal jealousy or professional bias. If it were a social club, it would be perfectly proper to vote against a man because he is personally distasteful, but where it is a scientific body responsible for the education of large numbers of young men and for the care of still larger numbers of hospital patients among the poor, even if a

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candidate were personally unfriendly I should vote for his election if he were the man best fitted for the place.

Turning now to the duties and responsibilities peculiar to trustees of hospitals, let me point out the objects of a hospital.

First, the care and the cure of the sick and injured; secondly, the education of medical men and medical students; and thirdly, the promotion of knowledge, which, in turn, will inure all over the world to the more speedy and certain cure of the sick and injured, and so be of the greatest benefit to humanity.

In order to accomplish these three purposes, it is necessary that the hospital shall have sufficient funds to purchase ground, erect buildings, and provide a thorough material equipment. It is a great pleasure to me, as to you also, to note that throughout the length and breadth of the land the medical and surgical staff never tax the always inadequate resources of hospitals for any remuneration. They serve without pay, they give ungrudgingly and freely day and night to the poor often for many years, their time and skill, without ever a thought of any money reward. Their reward comes from increased knowledge and skill, and the daily blessing invoked of heaven, often lisped in children's prayers or breathed in mothers' benisons which pass not unheeded by the Recording Angel.

But, as I have pointed out elsewhere, instead of receiving any pay, they give to hospitals. The mere money value of this daily gift of the profession to the poor amounts to an enormous sum. The value of the professional services of the staff of the Jefferson Medical College Hospital, a single hospital in a single city, on a moderate basis of fees, I found was more than half a million dollars annually. The millions upon millions of money given in that most self-sacrificing form—personal service—by the entire profession all over the United States, and I might add with still further pride, all over the world, is simply incalculable. The Gideon Grays and Weellum MacLures are not found only in Scotland or at the country-side. They are even more plentiful in the slums of our great cities, giving of their time, their skill, and what is more, their hearts, their lives, themselves to the service of humanity.

Trustees sometimes seem to take it for granted that their duties are ended when they have done two things: begged or given and safely invested the necessary funds, and then elected the staff. To my mind, their duties do not by any means end at this point. They should see to it that the resources of the hospital are utilized to the utmost in doing the largest good.

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Let us see now how the objects of a hospital, as I have stated them, can be realized. The first object is the care and cure of the patients. But the cure of any individual patient is not the "be all and the end all" of a hospital. His cure must be a means of larger vision to the doctor, who will thus be better fitted to care for future similar cases. Even his death, if he cannot be cured, should minister to the increasing knowledge and skill of the doctor so that he may be able to snatch future victory from present defeat.

The second—the training of doctors and students—is frequently carried out, but sometimes even objected to. There are three classes of doctors who are trained by a hospital: first, the staff of the hospital itself. I have lived through the period of the establishment of hospitals in many of the smaller cities and towns, and in some cases even villages in this country, for it was a rare thing in my early professional life for any except the larger cities to have hospitals. The moment that a hospital is established with its medical and surgical staff, that moment a new era has dawned on the *community* in which the hospital is established. More careful methods are introduced, greater cleanliness is observed, hygienic conditions are bettered, laboratory methods are inevitably introduced in time. Even if the old-timers who graduated years before our modern laboratory methods were adopted do not care for them or cannot use them, the young fellows who come fresh from our medical schools and serve as residents, and even the nurses graduated from our training schools, finally shame the older ones into better ways and greater exactness, not only in the hospital, but in their private work as well.

As a consequence of the establishment of these hospitals and the added skill and training of the local physicians and surgeons, the character of the consultations of the physicians and surgeons of our great medical centers has been greatly modified. The really simple cases, such as hydrocele and small tumors (and even large ones), clubfoot, harelip, etc., which used to be sent to city consultants, are now successfully operated on by the local surgeons, and only the more difficult, serious, or complicated cases are sent to the cities. This is a great advantage to the patient, whose good is the first consideration, and to the local medical men; and though seemingly a serious loss to the city consultant, it is in the end an advantage, as he must prove his better metal in the higher scientific fields and be, as well as seem to be, the better man.

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Moreover, the trustees of every hospital should see to it that a good library and laboratory are provided. Insensibly the staff will read more and more. A single restless progressive spirit, even though it be a young interne, calling attention to this case and to that, in one journal or another, will compel the rest of the staff to read in spite of themselves. It is absolutely clear that a laboratory with modern equipment for bacteriological, pathological, and chemical research in its examination of tumors, of the urine, the sputum, the feces, the blood, the pus, and other fluids from wounds, etc., is a necessity in every hospital. Even many of our smaller hospitals are equipped with microscope and reagents if not with a complete bacteriological outfit, which nowadays is inexpensive and imperative. All of this raises the intellectual and professional standard of the staff. I venture to say that no town of 20,000 people can afford to be without its hospital for the sake of its *own citizens,* utterly irrespective of the good it does to the poor who are treated in its wards. It must be established in the interest of the *well-to-do citizens* and their families, so that they may secure better equipped doctors for themselves as well as for the patients in their hospital. Self-interest, therefore, will compel every community to establish its hospital, even if charitable motives had no influence.

Again, the trustees of all hospitals of any size should establish a training school for nurses. Only those who, like myself, have lived in the period before such training schools were established, can appreciate the vast improvement effected in a hospital by this change. To replace the former ignorant, untrained attendants by "trained nurses whose jaunty caps and pretty uniforms and often winsome faces almost make one half wish to be sick, and when one is sick, half loath to be well," is not only a boon to the patients but to the doctors as well. The intelligent, well-trained nurse, who is on the alert to observe every important change of symptoms and who will keep accurate bedside notes, is the doctor's right hand. Not a few patients who would otherwise lose heart and hope are, one may say, lured back to health and happiness by the tactful attentions and restful but efficient care of such a nurse. The community of the well-to-do also are benefited, because the hospital provides them with skilled nurses in their homes when they are so unfortunate as to be compelled to remain there instead of going to the hospital.

The old repugnance to entering a hospital when sick or when an operation is demanded is rapidly fading away. The immense advantages of a good hospital over the most luxurious home are now

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acknowledged on all hands. The poorest patient in a hospital is better cared for, his case more carefully investigated by bacteriological, chemical and clinical methods in a hospital, than are the well-to-do in their own homes. Indeed, wise surgeons, except in cases of emergency, now very properly refuse to do operations in homes instead of in hospitals. In many instances lives that would be lost in homes are saved in hospitals, where the many and complex modern appliances for every surgical emergency are provided.

The hospitals in direct or indirect connection with medical schools, however, do a far larger work than merely the training of their own staff of doctors. They train three other classes of doctors: First, the undergraduates who are aspiring to the degree; secondly, graduate physicians who spend a certain amount of time in the hospitals either as internes or as temporary students refurbishing their professional knowledge; and thirdly, experts in certain branches of medicine and surgery.

The undergraduates are taught first in the general clinics, where to some extent they learn both by didactic instruction and by seeing the patients, hearing their histories, and witnessing the institution of proper treatment by prescription, by regimen, or if necessary, by surgical operation. This is of great value, particularly in the more important cases, and especially, for I speak now as a surgeon, in important operations. It is often objected that students see nothing in large clinics. To some extent this holds good; but no student can look on at an operation when the jugular vein or the lateral sinus is torn, the pleural cavity opened, the bowel lacerated, or other of the great emergencies of surgery occur, and fail to be impressed by the coolness of the operator, the carefully explained methods adopted for remedying the mischief, and the various devices used to save life, all of which hereafter will be used by him when similar emergencies may occur.

Yet far more important than the public clinics are the smaller clinics held with classes of ten to twenty men each, when under an experienced teacher the absolute work of the clinic is divided among the various students in turn, watching the pulse and the respiration, giving an anaesthetic, assisting actively at operations, percussing the chest, palpating the abdomen, determining inequalities of the surface or the varying density of underlying organs. Here is the real forum in which our modern medical student acquires his skill. In many cases visits in the ward itself are made, and to a small group around the bedside the physician or surgeon will point out

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the phenomena to be recorded, the need for the examination of the blood, the results of bacteriological cultures, the facts discovered by the microscope, or the chemical reagent. By the Socratic method also, he will reveal to the student the imperfection of his knowledge, call out—e-ducate—his powers of observation, of reasoning; stimulate his thought, and give him an impetus which will last throughout life. Who that has "walked the hospitals" with a Skoda, a Trousseau, a Nélaton, a DaCosta, or a Mitchell can ever forget their teaching?

It is sometimes objected by those who are not familiar with the actual facts, and especially by trustees, that this method of actual bedside instruction does harm to the sick. I speak after an experience of nearly forty years as a surgeon to a half dozen hospitals and can confidently say that I have never known a *single patient* injured or his chances of recovery lessened by such teaching. Of course, the physician or surgeon uses common sense. He would not allow a number of men to palpate the abdomen of a patient with peritonitis, or move an acutely inflamed joint, nor would the physician allow a patient with pneumonia to have the chest unduly exposed, or a typhoid fever patient disturbed if his condition was such that it would be inadvisable. But such cases are the exception. In fact, many of you are familiar with patients who have responded to repeated percussion by members of such a class by prompt recovery, attributed by the patient to the supposed medication of percussion. Moreover, it is by this actual practice only that the student acquires the necessary skill in the use of modern instruments of precision, such as the stethoscope, the laryngoscope, the esthesiometer, the sphygmomanometer, the various specula. Here he learns when to make blood counts, how to take histories, arrive at the actual facts by skillful cross-questioning, note the varying symptoms and physical signs of a case, determine the need for laboratory investigations, all under the guidance of skilled observers, who will point out his errors, encourage his queries, and stimulate his thought.

Moreover, trustees may overlook one important advantage of a teaching hospital. Who will be least slovenly and careless in his duties, he who prescribes in the solitude of the sick chamber, and operates with two or three assistants only, or he whose every movement is eagerly watched by hundreds of eyes, alert to detect every false step, the omission of an important clinical laboratory investigation, the neglect of the careful examination of the back as well as of the front of the chest, the failure to detect any important physical

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sign or symptom? Who will be most certain to keep up with the progress of medical science, he who works alone with no one to discover his ignorance; or he who is surrounded by a lot of bright young fellows who have read the last *Lancet,* or the newest *Annals of Surgery,* and can trip him up if he is not abreast of the times? I always feel at the Jefferson Hospital as if I were on the run with a pack of lively dogs at my heels. I cannot afford to have the youngsters familiar with operations, means of investigations or newer methods of treatment of which I am ignorant. I must perforce study, read, catalogue, and remember; or give place to others who will. Students are the best whip and spur I know.

Of the value of training graduates in postgraduate work I need scarcely speak, to this audience at least. The doctor who graduated five, ten, or fifteen years ago comes to our great centers of medical education and renews his youth at the fountain of knowledge. He learns the use of all the new instruments, sees new methods of operation, new methods of treatment, new means of diagnosis, and goes home an enormously better equipped man.

The trustees should see that the staff does not become fossilized by following the same ancient local methods from year to year, but should encourage them to visit other hospitals, see other men operate, hear other men discourse on the latest methods of investigation, and then import into their own hospitals all the good found elsewhere. I learn a deal by such frequent visits to the clinics of my brother surgeons, and if one who has grown gray in the service can thus learn, surely the younger men can do so. When we are too old to learn we are too old to remain on a hospital staff.

I do not know anything which has more impressed upon me the enormously rapid progress which surgery is making than a recent experience. I was absent from this country for almost a year and a half. In that time circumstances were such that I saw almost no medical journals and but few doctors. I have been home now eight months and even with incessant work I have not yet caught up, so rapid has been the progress of surgery in this short time. Had I been absent for five years, verily I should have been a "back number," and never could have caught up at all.

In his very excellent Presidential address before the Association of American Physicians in 1901, Professor Welch made a plea for hospitals to afford "the requisite opportunities to young men who aim at the higher careers in clinical medicine and surgery." He called attention to the fact that in our bacteriological, pathological

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and anatomical laboratories the opportunities, though still too few, were reasonably good, and in a few places exceptionally good, for the training of young men for positions as teachers of anatomy, pathology, and bacteriology. Any young man in these departments who by good hard work makes for himself a name is fairly sure, before long, of being called to some important post as a professor, director of a laboratory, or some similar position. But the facilities for work in clinical medicine and clinical surgery are far more restricted, since opportunities for both the exercise of their clinical skill are less frequently open to them and the possibility of combined physiological, pathological, bacteriological and anatomical research along with their clinical work is but scantily provided for. This plea is reinforced by the recent paper of Sir Michael Foster (*Nineteenth Century,* January, 1901, p. 57.) These special graduates, bright young men, determined to devote themselves to one or another department of medicine or surgery, are the men who bring honor to the school at which they obtain their training, and are invaluable to the community. They are the future Jenners, Pasteurs, Virchows, Listers, DaCostas and Grosses, and our hospitals should provide for these exceptional men exceptional facilities.

The third object of a hospital is the promotion of knowledge, and so, fourthly, the good of humanity. Physicians and surgeons engaged only in private practice do not generally keep notes of their cases, and rarely publish important contributions to knowledge. I find of 100 books taken consecutively in my library that 85 were written by hospital men and only 15 by authors not connected with any hospital so far as was indicated on the title page.

In order that proper investigations may go on, trustees should enforce a permanent record of all the cases treated in the hospital, properly indexed, from which the staff may derive their data for papers and books. Each large hospital should have its pathological resident as well as the clinical residents in the various wards, so that postmortem records shall be well kept, pathological, bacteriological, and chemical investigations of various secretions, blood counts, etc., shall be properly made and permanently recorded in such a manner as to be accessible.

It is too often the case that trustees, as I have said, regard their duties and responsibilities at an end when they have taken care of the funds and elected the staff. They may say that after all this is their real duty, and that all that I have advocated is medical and surgical, and the responsibility for it should devolve on the

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staff and not on the trustees. I do not take so narrow a view of the duties of trustees. When they have elected a physician or surgeon, if he neglects his duty, it is their business to displace him and fill his place with another man who will attend to his duty, and the duties that I have indicated pertaining to the increase of knowledge as well as of its diffusion are quite as much within their province as it is to see that the funds are invested to the best advantage. The intellectual funds as well as the invested funds must bring in good dividends.

If trustees and staff work together for such a purpose and in such a manner, they will create an ideal hospital which will do more good to the patients than any other type of hospital. It will attract the best physicians and surgeons in every community, will acquire the best reputation, not only local, but it well may be national, and do the most for the good of science and the benefit of humanity.

It may be said that this is an unduly strenuous view of the duties of trustees, that in our father's day and in our own earlier lives no such conditions existed or were contemplated. "I need hardly ask a body like this," said President Roosevelt in addressing the Methodists assembled in council, "to remember that the greatness of the fathers becomes to the children a shameful thing if they use it only as an excuse for inaction instead of as a spur to effort for noble aims. . . . The instruments with which and the surroundings in which we work have changed immeasurely from what they were in the days when the rough backwoods preachers ministered to the moral and spiritual needs of their rough backwoods congregations. But if we are to succeed, the spirit in which we do our work must be the same as the spirit in which they did theirs."

Moreover, we must remember that "the world-field into which all nations are coming in free competition by the historical movement to which all narrower policies must sooner or later yield, will be commanded by those races which, in addition to native energy and sagacity, bring the resources of scientific investigation and of thorough education." The international race for the leadership of the world is just as strenuous and intense in medicine as it is in commerce. If we are going to join the race and win the prize there must be the highest development of American education at the top. The best men must be pushed to the front, and ample opportunities for growth, for investigation and for original research must be provided. Never has there been so large an opportunity for the man of large ideas, complete education and indomitable energy and pur-

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pose as there is to-day. The world is waiting, looking, longing for him, and will cry "Make room" for him when he is found.

In the hands of the trustees of our colleges and hospitals are the money and the opportunity for developing such men. If the right spirit pervades both trustees and medical faculties and hospital staffs, then it will be but a short time before America will lead the world in medicine as well as she now does in commerce.

Will the profession rise to the level of their great opportunity? Yea, verily they will! Never yet have they been wanting when the emergency arose; not only the emergency of labor, but also the emergency of danger.

In Russia the common soldier counts for little. Yet in Vladikavkaz (where the Dariel Pass—the old Portæ Caspiæ of Herodotus—leading from the Caucasus joins the railroad from Baku on the Caspian to Moscow) is a monument to a common soldier. At the last battle in which the Russians won the victory over Schamyl which gave them undisputed sway over the Caucasus, this soldier blew up a mine and won the day at the cost of his own life. It was ordered that his name should never be erased from the list of his company. At every roll-call when his name is reached, the solemn answer is given, "Died in the service of his country."

In our hospitals lurk the deadly breath of diphtheria, the fatal virus of bubonic plague, of cholera, of yellow fever, of typhus fever, and the ever present danger of blood poisoning. I have known of brother physicians who have died victims to each one of these scourges. Yet who has ever known one of our guild to shrink when danger smote him on the right hand and the left and death barred the way? As brave as the Russian soldier, ready to risk life, and, if need be, to lose it, these marytrs to duty shall never have their names stricken off the honor list, and at the last roll-call the solemn reply shall be, "Died in the service of humanity."

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